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PNEUMOENCEPHALOGRAPHY AND THE DEVELOPMENTAL DIAGNOSIS OF BEHAVIOR

AN ANALYSIS OF 53 CASES OF CEREBRAL PATHOLOGY

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IN THE outpatient and consulting service of the Yale Clinic of Child Development, 53 cases have been collected in which it is possible to correlate the findings on developmental examination with the findings on pneumoencephalographic examination. Most of the children were seen in consultation with the pediatric department of the New Haven Hospital, and the x-ray studies were made by the x-ray department* of the same hospital. A small number were referred to us from private sources and brought with them the reports of encephalographic studies made elsewhere.

For convenience the cases are presented in the following seven alphabetically designated groups based on the *clinical* diagnosis: A. Congenital Malformations and Aplasias; B. Cerebral Degenerative Disease; C. Epilepsy; D. Hydrocephalus; E. Cerebral Injury; F. Postmeningitis; G. Postencephalitis.

Each clinical group is presented in condensed tabular form, has discussion and comment, and is illustrated by selected, representative x-ray films. The tables give for each case the history and physical findings at the time the child presented himself for developmental study, the pneumoencephalographic diagnosis, the developmental status, and subsequent developmental course when known.

In some instances the clinical classification is somewhat empirical. Etiology is often obscure, and the distinction between primary and secondary brain affections often cannot be made; there is as much evidence one way as another. In all instances, I assume full responsibility for the diagnostic classification.

*Dr. Hugh Wilson kindly reviewed a large number of the films. Without his generous assistance and cooperation this study would not have been possible.

TABLE I

A. CONGENITAL MALFORMATIONS AND APLASIAS

CASE	SEX AGE	CLINICAL HISTORY	PHYSICAL FINDINGS	ENCEPHAL. EXAM.	DEVELOPMENTAL STATUS	
					EARLY STATUS	FOLLOW-UP
A1	M 16 wk.	Normal birth; deformity lower jaw and profuse nasal discharge from birth; at 2 wk. high fever and convulsion; at 2 mo. high fever again	Persistent twitchings; arms rigidly flexed; bilateral ankle clonus; tonic Babinski, hyperactive reflexes; very irritable	No subarachnoid air; dilatation ventricles; large porencephalic cyst right frontal, communicating with lateral ventricle; cerebellar atrophy; cavum septum pellucidi; cavum vergae	16 wk.—Idiot	Died at 19 wk. (Autopsy revealed marked cerebral atrophy, enormous bilateral porencephalic cysts replacing both frontal lobes)
A2	F 18 wk.	Sibling hydrocephalic; normal birth, good physical progress, but vision and responsiveness questioned	Essentially negative	No subarachnoid air; dilatation ventricles; deformity ventricles; fagenesis corpus callosum	18 wk.—Idiot	
A3	F 26 wk.	Sibling died of congenital heart disease; birth weight, 9 pounds, 12 ounces; respiratory stridor, hypertelorism; progress only fair, very obese	Hypertelorism; obese; overgrowth	Moderate dilatation ventricles; cerebral hypoplasia	26 wk.—Level of 16 wk. (Unclassified)	40 wk.—Level of 28+ wk. 15 mo.—Level of from 32 to 36 wk. 24 mo.—Level of from 32 to 36 wk. (*Imbecile-Idiot)
A4	M 17 mo.	Normal birth, resuscitated with difficulty; oxygen tent for three days; hypospadias; poor progress; convulsions at 16 mo. with varicella	Head small; hypospadias; strabismus; hyperactive reflexes	Dilatation ventricles; cortical atrophy (micro-macrogyria); fifth ventricle; agenesis corpus callosum	17 mo.—Level of 16 wk. (Idiot)	

A5	F 22 mo.	Normal birth; birth weight, 5 pounds, 14 ounces; nasal obstruction noted from birth interfering with feeding; poor progress; at 11 mo. nasal encephalocele removed and cribriform plate repaired, complicating osteomyelitis frontal bones	Healing sinus over frontal bone	Left ventricle dilated; cisterns dilated; cortical atrophy left frontal; porencephaly left frontal	22 mo.—Level of 10 mo. (Imbecile-Idiot)	27 mo.—Level of 10 mo. 38 mo.—Level of 10 mo.* 42 mo.—Chronic recurrent convulsions
A6	M 19 mo.	Normal birth, fontanel closed at birth; never any progress; convulsion at 18 mo.	Synostosis cranii; testes undescended; reflexes hyperactive; extremities slightly rigid; irritable	Slight dilatation ventricles; extensive cortical atrophy; cerebellar atrophy	19 mo.—Level of from 24 to 28 wk. (Imbecile-Idiot)	
A7	F 28 mo.	Normal birth, no illness; always retarded	Strabismus; hearing defect	Dilatation ventricles (no further report)	28 mo.—Level of 20 wk. (Idiot)	
A8	F 34 mo.	Twenty-four hour labor, forceps delivery; birth weight, 5 pounds, 13 ounces; always retarded, irritable	Poorly developed; small head (43.5 cm.); no neurologic signs	Dilatation ventricles; marked cerebral atrophy; marked cerebellar atrophy	34 mo.—Level of from 8 to 12 wk. (Idiot)	Died of pneumonia at 4 yr.
A9	F 45 mo.	Ninth child; birth weight 6¾ pounds; labor, sixty-five minutes; excessive amniotic fluid; normal neonatal period; quiet, unresponsive infant; poor progress	Poorly developed; reflexes normal; coarse tremor involving head, trunk, and all extremities	Cortical atrophy; ventricles normal	45 mo.—Level of 28 wk. (Idiot)	
A10	M 6½ yr.	Normal birth; has always been backward; pneumonia at 3 yr.; scarlet fever at 4½ yr.	Essentially negative	No air in ventricles; sulci and cisterns not unusual; indeterminate	6½ yr.—Level of from 24 to 30 mo. (Imbecile)	

*The term Imbecile-Idiot is used to indicate that future development may continue at an imbecile level or may drop to the idiot level.

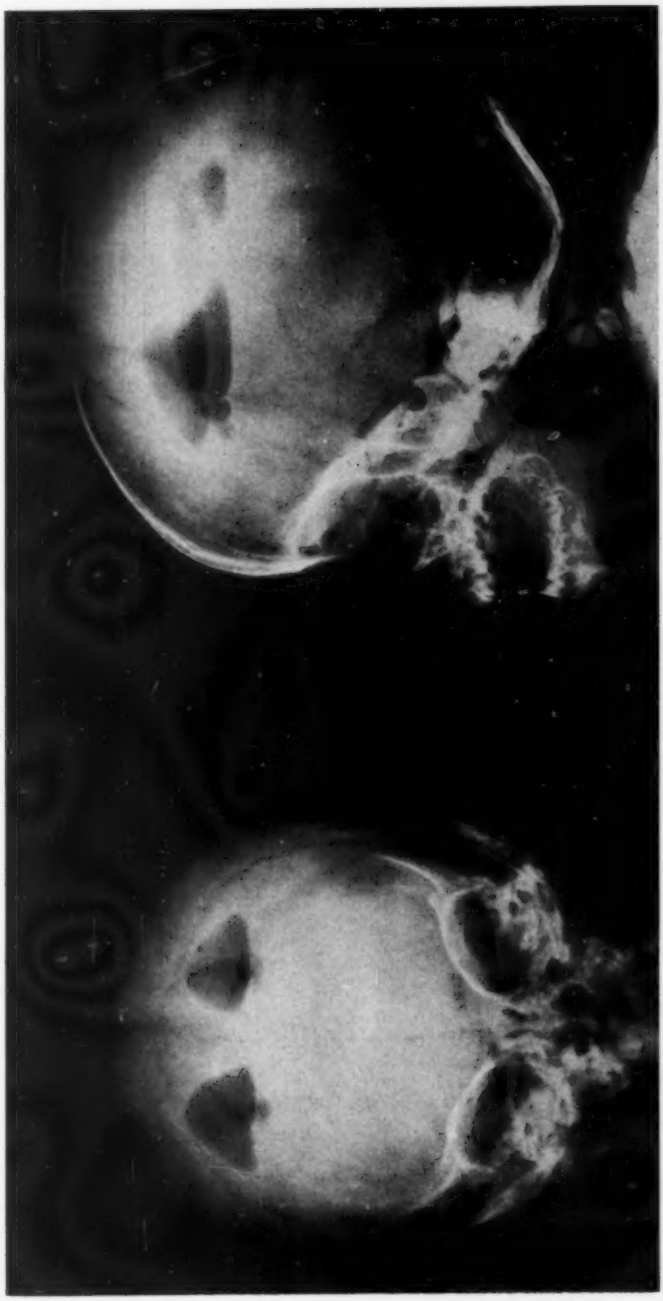
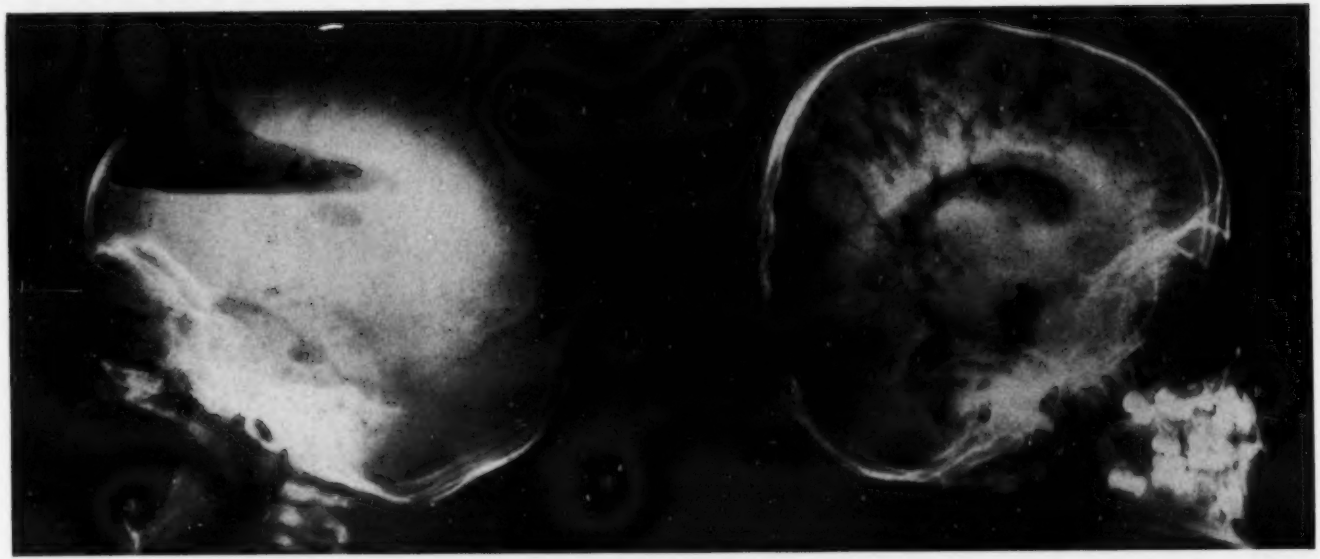


Fig. 1.—Case A2, 18 weeks of age (idiot). Posteroanterior and lateral films show widely separated lateral ventricles with unusually high position of roofs of lateral ventricles. The characteristic deformity, dilatation, and wide separation of the lateral ventricles are highly suggestive of congenital absence of the corpus callosum.



A. *B.*

Fig. 2.—*A*, Case A1, 16 weeks of age (idiot). The film shows a large cyst intervening between the right anterior horn and the squamosal portion of the right frontal bone. The cyst communicates with the right lateral ventricle (shown by the rapid shift of air into the ventricular system with change of head position).

B, Case A8, 34 months of age (idiot). The lateral ventricles are symmetrically dilated; the fourth ventricle is huge. All the cisterns are large, particularly the cisterna magna. The cerebral sulci are abnormally large and wide. Internal hydrocephalus ex vacuo and marked cerebral and cerebellar atrophy.

A. CONGENITAL MALFORMATIONS AND APLASIAS

This somewhat motley assortment of cases is grouped together because of the primary nature of the defect in each instance. Four children show congenital cerebral malformations: Case 1, porencephalic cyst; Case 2, agenesis corpus callosum; Case 4, agenesis corpus callosum, micro-macrogyria; Case 5, porencephaly, nasal encephalocele.

Case 3 is an example of a rather uncommon syndrome: hypertelorism associated with maldevelopment of the sphenoid bone (and presumably also the pituitary gland), obesity, overgrowth, and progressive retardation with final idiocy.

The infants in Cases 1, 3, and 4 have malformations of other body parts. In Case 3 the infant had a sibling with congenital heart disease, and in Case 4 the infant has a hydrocephalic sibling. This child also had a poor birth reaction and his condition might easily be interpreted as a case of "birth injury." None of the children showed normal developmental progress at any time, though there is some evidence that after operation one child (Case 5) lost what developmental momentum she had. Neurologic signs were prominent only in the infant in Case 1. The outstanding feature in the infants in Cases 2 and 4 was the lack of normal responsiveness. Intracranial pathology was not suspected in the infant in Case 5 until removal of the nasal polyp resulted in seepage of cerebrospinal fluid. In all instances the pneumoencephalogram was invaluable in establishing the nature of the neuropathology.

Cases 6 to 9, inclusive, are examples of simple primary amentia of severe degree. In each infant the birth history is normal and the poor developmental progress dates from birth. In Case 6 the infant has an associated synostosis cranii; the infant in Case 7 is probably congenitally deaf. In Case 9 the infant probably has a cerebral and cerebellar aplasia, although the pneumoencephalographic report is incomplete. Cortical atrophy is almost universal in this group; cerebellar atrophy also is notable, together with some dilatation of the ventricles. Case 9 is the only example of the higher grades of mental defect; the x-ray findings show no outstanding abnormalities.

The whole group of ten cases is distinguished by the high percentage of congenital anomalies (80 per cent including all anomalies, 50 per cent excluding anomalies of the central nervous system), by the history of normal birth but of retardation dating from birth, and by the relative infrequency of convulsions as an essential symptom. Eight of the patients have siblings; in two instances (25 per cent) a sibling is also malformed.

B. CEREBRAL DEGENERATIVE DISEASE

Table II presents a rather homogeneous group of cases, the histories of onset, course, and outcome repeating themselves with tragic regularity. In this series there is a predominance of males, though females

are by no means exempt. Birth complications are unusual, and the early course of development is normal.* Convulsions begin very early in life, the average age of onset being about 3 months, and the range being from 1 to 6 months. The convulsions are usually generalized, not severe or prolonged but frequent, and without obvious precipitating cause. The infant may have as many as from three to thirty seizures daily. Shortly after the onset of convulsions, developmental progress ceases, behavior deteriorates, and idiocy supervenes.

Neurologic findings are very variable. Irritability is common, as are hyperactive reflexes and local or generalized twitchings. A few infants develop some rigidity. On pneumoencephalographic examination, cortical atrophy with concomitant moderate ventricular dilatation is the outstanding and most consistent finding.

The findings on developmental examination depend, to some extent, upon when in the course of the disease the examination is made, how rapidly deterioration is taking place, and when it began. Normal residuals may be apparent at first, but the end result is always more or less complete idiocy. The infant is either inert or irritable and almost completely unresponsive. In a few cases isolated fragments of normal behavior patterns may persist for months, quite out of context. As time goes on, the convulsive attacks may become less frequent or come in showers with long, free intervals in between. Any developmental progress that occurs is usually limited to the motor field; many of these children learn to sit alone, some to walk. Play remains infantile and may cauliflower at the infantile level into many bizarre and stereotyped forms. Speech is not developed. The head is usually small due to the lack of cerebral development. The occipital region tends to be flattened because of the long dominance of the supine posture.

Because the infant's behavior repertoire in the first few months of life is commonly ascribed to the functioning of subcortical structures, the validity of the early progress described in this syndrome is often questioned. It is postulated that the child is primarily defective but that the defect does not become apparent until it is time for the cortex to function. We are inclined to disagree in part at least with this interpretation. Much postural and motor behavior in the early months is doubtless mediated through subcortical channels. On the other hand, such exploitive behavior as ocular following, ocular "searching," ocular "grasping," early prehensory efforts, however unsuccessful, and early social behavior, such as responsive smiling and laughing, responsive vocalization, and initiation of social play, are all mediated by the imperfectly organized but developing cortex. Cortical activity does not appear suddenly in the sixth month and as suddenly take over the

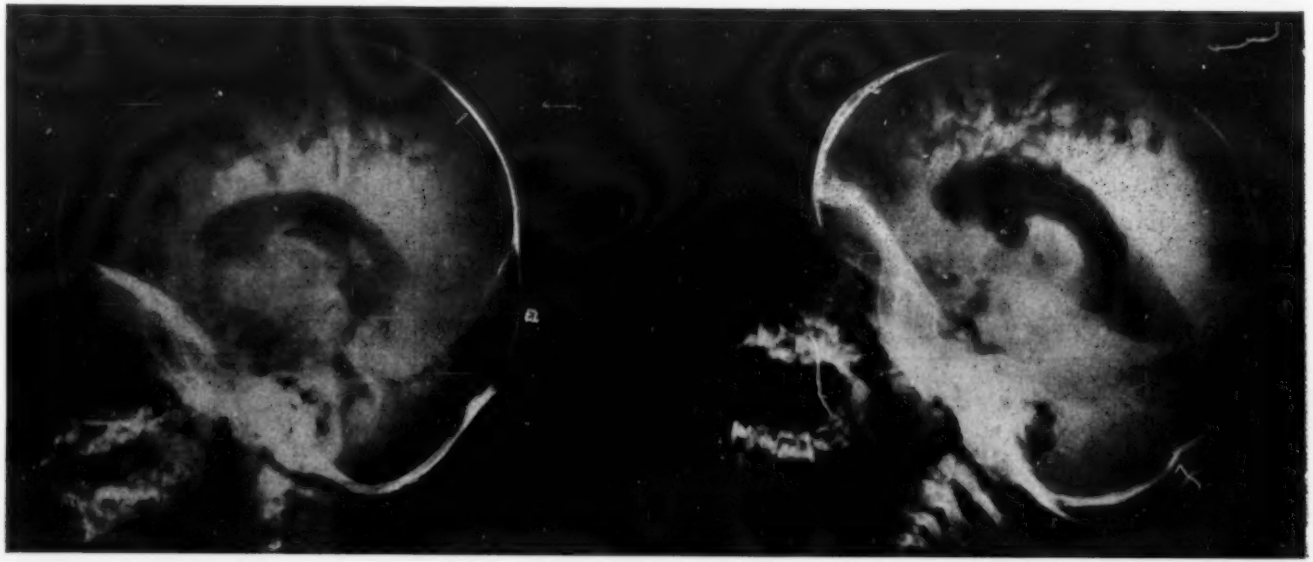
*In three of the eleven patients, one or more convulsions took place in the neonatal period, followed by a free normal interval before the onset of frequent, repeated seizures.

TABLE II

B. CEREBRAL DEGENERATIVE DISEASE

CASE	SEX AGE	CLINICAL HISTORY	PHYSICAL FINDINGS	ENCEPHAL. EXAM.	DEVELOPMENTAL STATUS	
					EARLY STATUS	FOLLOW-UP
B1	M 12 wk.	Resuscitated, cyanotic first day; normal first month then convulsions, 2 to 3 daily; increasing prominence occipital bone	Vacant expression, bulging occipital bone; reflexes hyperactive; irritable; head retracted; slight general rigidity	Localized bilateral cortical atrophy; ?obstruction in anterior portion of cisternal system	12 wk.—Idiot	
B2	M 13 wk.	Normal birth; birth weight, 9 pounds, 4 ounces; early normal progress though irritable; convulsions began at 13 wk., nine in four days	Irritable; quiet only in prone; otherwise negative	No subarachnoid air; mild dilatation ventricular system; otherwise indeterminate	13 wk.—Level of 8 wk. (Unclassified)	21 wk.—Level of 4 wk. 40 wk.—Level of 4 wk. 5 yr.—Level of 4± wk. (Occasional convulsion; idiot)
B3	M 23 wk.	Normal birth; birth weight, 4 pounds, 15 ounces; convulsion on fourth day with staphylococcus septicemia and jaundice; good recovery; normal progress to 4 mo. when convulsions (twitchings) began; these have continued	Head small, anterior fontanel, 1 finger tip; neck slightly stiff; grasp reflex weak; reflexes hyperactive	Dilatation ventricles; cerebral cortical atrophy	23 wk.—Idiot	46 wk.—Level of 4– wk. 20 mo.—Level of 4– wk. (Mod. general rigidity; convulsions have ceased; idiot)
B4	M 25 wk.	Normal birth; birth weight, 9 pounds; first convulsion at age of 5 weeks; development then normal to 24 wk., when severe recurrent convulsions began (20 to 30 daily)	Negative	Cerebral atrophy left; ?cerebral atrophy right; ?cerebellar atrophy	25 wk.—Level of 20 wk. (Normal range; will deteriorate)	48 wk.—Level of 28– wk. 18 mo.—Level of 28– wk. (Imbecile-Idiot)
B5	F 28 wk.	Fifth child; labor, 1 hour; early normal progress; convulsions began at 15 wk. 3 to 4 daily; behavior regressed	Occasional spasmodic jerking movements; bilateral ankle clonus; reflexes hyperactive	No subarachnoid air; dilatation lateral ventricles; dilatation cisterns; ?porencephaly right frontal	28 wk.—Idiot	

B6	M 37 wk.	Normal birth; thirteen convulsions on third day; normal development for three months; at 3 mo. convulsions recurred and continued, 4 to 5 daily; behavior regressed	Large head (49 cm.); stares; left eye slightly divergent. Movements and reflexes normal	Dilatation ventricles; cortical atrophy	37 wk.—Level of 8 wk. (Imbecile-Idiot)	30 mo.—Reported 2 to 3 mild convulsions weekly (Pulls to feet in play pen; does not grasp or play with toys; no words)
B7	F 40 wk.	Normal birth; convulsions began at 2 wk. increasing to 4 to 5 daily; development has regressed	Spastic diplegia—suggestion of forced grasping; reflexes hyperactive; unsustained ankle clonus	Dilatation ventricular system; bilateral cortical atrophy	40 wk.—Idiot	20 mo.—Reported fewer convulsions (Not sitting or standing; very retarded)
B8	F 41 wk.	Normal birth; weight 8½ pounds; easily resuscitated; normal development to 4 mo., then regression; had 14 convulsions between third and ninth month, then chronic convulsive state	Irritable; twitching; reflexes hyperactive	Marked dilatation of ventricles; marked cortical atrophy	41 wk.—Idiot	
B9	M 43 wk.	Normal birth; birth weight, 9 pounds; convulsions began at 3 wk., 5 to 10 daily, but development continued to 4 mo. then regressed; convulsions continue	Head small (44.5 cm.); otherwise negative	Marked cerebral atrophy; deformity left lateral ventricle; agenesis corpus callosum	43 wk.—Idiot	2 yr.—Reported worse
B10	F 25 mo.	Fraternal twin normal; normal birth; birth weight, 8 pounds; normal to 28 wk. when minor attacks began, accompanied by change in behavior; poor progress; attacks continue; occasional major convulsion	Hyperactive; stares; unsustained ankle clonus left; internal strabismus left; can sit and creep	Cerebral atrophy	25 mo.—Level of 28 wk. (Imbecile-Idiot)	7 yr.—Reported no attacks since 3 yr. (Walking but no words; bangs head; very retarded)
B11	M 25 mo.	Normal birth; weight, 6 pounds; one convulsion in neonatal period; normal progress to 6 to 7 mo. when convulsions recurred, 8 to 10 daily; development ceased; no convulsions since 16 mo. but no progress	Continuous purposeless movements; hypotonic	Slight dilatation of ventricles; cortical atrophy	25 mo.—Level of 32 wk. (Imbecile-Idiot)	30 mo.—Level of 32 to 36 wk. (Walking alone; idiot)



A. *B.*

Fig. 3.—*A*, Case B7, 40 weeks of age. Cerebral degenerative disease (idiot). Symmetrical dilatation of the ventricular system, asymmetrical distribution of subarachnoid air in widened spaces—cortical atrophy.

B, Case B8, 41 weeks of age. Cerebral degenerative disease (idiot). Marked dilatation of the ventricles with marked cortical atrophy.

operation of the organism. Cortical activity has beginnings and developments which are evident to the observer as soon as the beginnings and developments of behavior are understood.

Most parents, when carefully questioned, are able to give very convincing stories substantiating their claims of early normal progress ("held up his head and noticed things; laughed and smiled, played with his hands; watched everything and loved to be played with; played with his father's necktie"), and all insist that shortly after the convulsions began, development failed ("he stopped noticing; I don't know if he even sees any more; he stopped smiling and doesn't play; he can't even hold up his head now, and he was so bright before"). Case 4 is of particular interest and importance in this connection. Within the first week of the disease, the attending pediatrician described the infant as bright and alert between seizures; on developmental examination at 25 weeks of age he had attained a maturity level of at least 20 to 24 weeks, well above the "subcortical level." Purposeful behavior was evident in reaching for and grasping toys, retaining and exploiting them by mouthing and selective regard. He "talked to" the rattle in his hand and initiated vivid social play with the examiner. Attention, interest, and drive were of good normal quality. Five months later his behavior had lost all its normal character and was definitely disorganized and defective. At 18 months he could pull to his feet in his play pen, but he had no words, did not even discriminate strangers, and had no interest in toys.

Case 9 is included in this group, in spite of the evidence of congenital cerebral malformation (agenesis corpus callosum), because the history is fairly typical, and also because this malformation is not in itself incompatible with normal mental development.*

Differentiation between this syndrome and essential epilepsy is made on the basis of the much earlier age of onset in cerebral degenerative disease, the greater frequency of convulsions, and the rapid and invariable severe mental retardation. It is, of course, possible that the only essential difference is the age of onset; in other words, that which we call cerebral degenerative disease is actually epilepsy occurring in the first few months of life, the serious effects being due to the extreme youth of the patient. The question can hardly be answered on the available evidence; from a clinical standpoint there would seem to be real value in making the distinction because of the tremendous difference in the developmental outlook in the two conditions.

C. EPILEPSY

This group has proved, on analysis, to be one of the most interesting of all. In contrast to the other convulsive group (cerebral degenerative

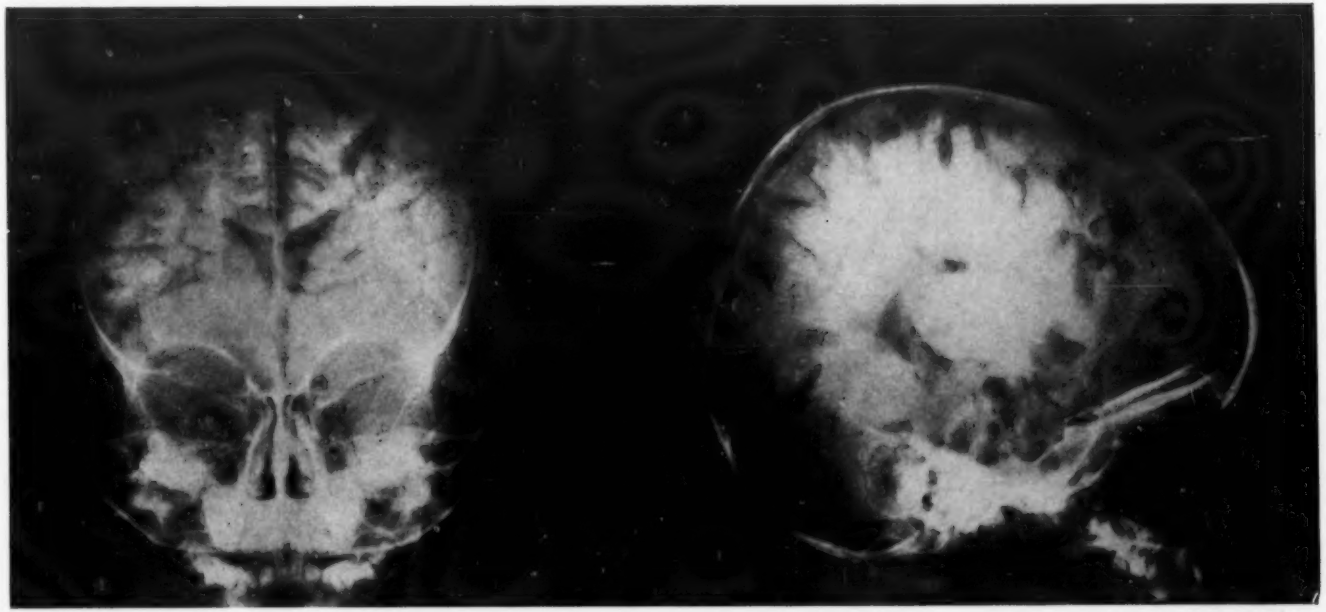
*Davidoff and Dyke[4] report a child of 6 years of age with an I.Q. of 107 in whom the diagnosis of agenesis of the corpus callosum was made by pneumoencephalography and confirmed at autopsy.

TABLE III

C. EPILEPSY

CASE	SEX AGE	CLINICAL HISTORY	PHYSICAL FINDINGS	ENCEPHAL. EXAM.	DEVELOPMENTAL STATUS	
					EARLY STATUS	FOLLOW-UP
C1	F 13 mo.	Normal birth; normal progress; at 1 year began sudden brief attacks of falling; recovers and resumes play as if unaware; minor attacks in showers	Negative	Bilateral cortical atrophy	55 wk.—Level of 48 wk. (Normal range)	15 mo.—Level of 48 to 56 wk. 21 mo.—Level of 18 to 21 mo. (Low average)
C2	F 15 mo.	Normal birth; well until 1 year when generalized convulsions began, at first several daily, then about twice a week	Bright and alert; no weakness; walks with support	Bilateral cortical atrophy	15 mo.—Level of 13 mo. (Normal range)	20 mo.—Level of 17 to 18 mo. 27 mo.—Level of 24 mo. 37 mo.—Level of 42 mo. (High average)
C3	F 16 mo.	Low forceps, fair cry after stimulation; at 43 wk. (normal progress) fell and struck head; at 45 wk. left-sided convulsion followed by transient hemiplegia; generalized convulsion at 14 mo.; left-sided convulsion with transient hemiplegia at 15 mo.; one minor episode at 24 mo.	Negative	Bilateral cortical atrophy	16 mo.—Level of 13+ mo. (Normal range)	24 mo.—Level of 24 mo. (Average)
C4	M 16 mo.	Precipitate birth; cyanotic attacks, difficulty breathing, oxygen tent four days; several small transfusions; gained poorly first 3 months; strabismus marked; sat at 7 mo., walked at 14 mo.; left-sided convulsion at 16 mo.; severe generalized convulsion at 20 mo.	Postseizure; irritable, dull; marked strabismus; awkwardness left hand, little use right; later, no findings except strabismus	(20 mo.) Dilatation lateral ventricle; minimal cortical atrophy	16 mo.—Level 12 to 13 mo. (Normal range)	18 mo.—Level of 18 mo. 24 mo.—Level of 21+ mo. (Low average)

C5	M 17 mo.	Normal birth; birth weight, 4½ pounds; ever since birth has had fainting spells; cries, goes limp, turns blue, then white; after attack confused, tremor of hands; stands and walks well	Head asymmetrical; reflexes normal; hemangioma left buttock and right forehead	Minimal cortical atrophy	17 mo.—Level of 15++ mo. (Low average)	33 mo.—Level of 30 mo. (Low average)
C6	M 19 mo.	Normal birth and neonatal period; always holds breath with crying; normal progress; convulsions with pneumonia at 11 mo.; convulsions with tonsillitis at 14 mo.; eight subsequent convulsions, some associated with illness, some not	Negative	Dilatation cisterns; minimal dilatation ventricles; bilateral cortical atrophy	19 mo.—Level of 15 to 18 mo. (Normal range)	24 mo.—Level of 24 mo. (Average)
C7	F 42 mo.	Normal birth; weight, 10 pounds; minor attacks began at 3 mo.; several daily for 6 weeks, then free interval of 2 mo. followed by recurrence; normal progress; walked at 11 mo.; singing little songs at 13 mo.; encephalogram at 15 mo.; reported normal; deteriorated after this hospitalization; grand mal attacks began at 39 mo.	Hyperactive; †visual defect; some clumsiness in use of right foot	No subarachnoid air; indeterminate	42 mo.—Level of 10 to 11 mo. (Imbecile)	
C8	M 43 mo.	Normal birth; weight, 8 pounds, 3 ounces; normal progress; first convulsion at 2 yr.; occurred every 2 weeks for 6 months; remission of 6 months, then recurrence	Arms and hands twitch frequently; occasionally "absent"	Dilatation ventricular system; dilatation basilar cisterns; minimal cortical atrophy, right	43 mo.—Level of 36 to 42 mo. (Slightly clouded state; potentially normal if convulsions controlled)	Since 3 yr. and 3 mo. has constant twitchings as well as full seizures; convulsions almost constant during next 3 years, with deterioration 7 yr.—Level of 18-mo. (Grossly deteriorated; idiot)



A. *B.*

Fig. 4.—*A*, Case C1, 15 months of age. Petit mal, low average development. Ventricular system does not show any appreciable degree of dilatation. Subarachnoid air over surface of both hemicrania show large sulci—cortical atrophy.

B, Case C2, 15 months of age. Grand mal, high average development. No dilatation of the ventricular system. Considerable collection of subtentorial air, left. The marked increase in width of subarachnoid markings indicates cortical atrophy.

disease), the children are older when the disease begins. Males and females are equally divided. The seizures may be either of the petit mal or grand mal type, or both; when grand mal attacks are present, they are much less frequent and much more severe than in cerebral degenerative disease. The condition is presumably primary or "idiopathie" in all the reported cases, though possible etiologic factors need consideration in Cases 3 and 4.

The infant in Case 3 has a history of minor trauma to the head two weeks before her first convulsion; two convulsions were unilateral and followed by transient hemiplegia, one was generalized. The pneumoencephalogram shows evidence of diffuse pathology (cortical atrophy). Neurologic examination is entirely negative between attacks. Clinically the trauma is not considered significant; it was too mild, there were no immediate evidences of injury, it antedated the convulsion by too long a period. Actually, it is surprising that more parents do not give similar stories—minor accidents are so frequent in the first two years.

In Case 4 the infant has a birth and neonatal history that cannot be entirely ignored. His first convulsion was unilateral, his second generalized. Physical findings between attacks are limited to the marked strabismus. The pneumoencephalogram shows evidence of diffuse mild pathology. In this case the possibility of intracranial damage at birth cannot be excluded. He is included in this group, none the less, because of the lack of deterioration and relative clinical consistency with the other cases.

The outstanding feature of this group is the conflict between pneumoencephalographic findings and behavior development. In contrast to the children suffering from cerebral degenerative disease, where x-ray evidence of extensive pathology is supported by clinical evidence of abnormal, deteriorated behavior, revealed by developmental examination, and proved by the subsequent course of events, in this group there is no such agreement.

In all but one instance the x-ray clearly indicates generalized cerebral atrophy, marked in four children and minimal in three, but behavior development is entirely normal on the first examination. The one child (Case 7) who is retarded and deteriorated has "indeterminate" x-ray findings. All of the seven normal children with cortical atrophy have had follow-up examinations: Case 8 had almost continuous convulsions for almost three years, occasionally so severe that he was semiconscious for days. As might be expected, behavior has deteriorated to a marked extent. The other six children have all had irregular interval seizures since their first visit; all are doing well. The child in Case 2 has been followed for two and one-half years and has even raised her status a little above the average.

This seems to us to be a very important matter, particularly because some of these children had been given a hopeless prognosis on the basis

TABLE IV

D. HYDROCEPHALUS

CASE	SEX AGE	CLINICAL HISTORY	PHYSICAL FINDINGS	ENCEPHAL. EXAM.	DEVELOPMENTAL STATUS	
					EARLY STATUS	FOLLOW-UP
D1	F 8 wk.	Instrumental delivery, mark over eye and on cheek; birth weight, 6 pounds, 3 ounces; head, 14 inches; did not nurse well; fever 3 to 4 days; fifth day, fontanels wide, head size slowly increasing; at 9 wk. and 12 wk., removal of choroid plexus	Sutures widely separated, definitely hydrocephalic; head circum., 16 inches; temporal veins prominent; hydrocephalic squint; head retracted, neck slightly rigid; ?visual defect	Marked obstructive hydroceph.; obstruction at distal extremity, fourth ventricle; no filling cisterns or sulci	8 wk.—Fetal responses (Unclassified)	Died at 12 wk. (postoperatively) (Autopsy: Fibrous adhesions in cisterna magna, obstruction foramina of Luschka and Magendie)
D2	M 23 wk.	Normal birth; normal progress to 16 wk., when meningococcic meningitis developed; treated with serum; recovery with progressive hydrocephalus and blindness; at 33 wk. and 36 wk., removal of choroid plexus with arrest hydrocephalus	At 16 wk., head retracted, back rigid, fontanel bulging and tense, positive Kernig; purulent spinal fluid with meningococci; 25 wk., anterior fontanel, 7 × 7 cm.; sutures separated, internal strabismus, hydrocephalic squint; blind	At 26 wk., marked hydrocephalus; no subarachnoid air; ?adhesive arachnoiditis	23 wk.—Level of 12 wk. (Unclassified; blind)	28 wk.—Level of 8 to 12 wk. 38 wk.—Idiot 14 mo.—Idiot
D3	M 26 wk.	Normal birth; no progress from birth; at 24 wk., convulsions and subarachnoid hemorrhage followed by progressive hydrocephalus; at 32 wk. and 40 wk., removal of choroid plexus	At 24 wk., fontanel bulging and pulsating; pupils wide, neck slightly stiff; left hemiparesis	(Postoperative) No subarachnoid air; dilatation of ventricles; enlarged cisterna magna; ?adhesive arachnoiditis	26 wk.—Idiot	Report at 1 yr.—No progress; huge head 3½ yr.—Died

D4	M 38 wk.	Normal birth; birth weight, 6 pounds; lethargic first week, fed by gavage; at 5 wk. had cyanotic attack with vomiting; since then frequent, forceful vomiting; weak; slow progress	Thin, underdeveloped, malnourished; movements weak; noticeably hydrocephalic; head circumference, 44.2 cm.; anterior fontanel, 5 × 5 cm., tense; posterior fontanel, 1 finger; hydrocephalic squint	Ventricles uniformly dilated; basal cisternae large; cortical atrophy	38 wk.—Level of 32 wk. (Normal range; normal quality)	20 mo.—Low average (Arrest of hydrocephalus)
D5	F 19 mo.	Sibling has clubfeet; labor, 16 hours; head arrested at outlet, low forceps; respiratory difficulty, 24 hours; normal development to 14 mo., then had measles and chickenpox, after which sat poorly, legs became stiff, head large (enlargement of head began before illness)	Head circumference, 53 cm.; anterior fontanel, 4 fingers; hydrocephalic squint; legs spastic, reflexes hyperactive; bilateral choked discs	Marked dilatation of ventricular system and cisterna magna; block at incisura or chiasmatic cisterns probably; no subarachnoid air	19 mo.—Level of 15 mo. to 18 mo. (Normal range)	Died following attempt at operative relief
D6	F 30 mo.	Sibling microcephalic; normal birth, occipital meningocele; progressive hydrocephalus with arrest; at 2½ yr. excision and repair of meningocele	Strabismus; hydrocephalus	Hydrocephalus; cortical atrophy	30 mo.—Level of 24+ mo. (Dull-normal)	4 yr.—Dull-normal 5 yr.—Dull-normal
D7	M 32 mo.	Delivered by version and extraction; birth weight, 7 pounds; no neonatal difficulties; insidious change in facies and gradually increasing anorexia began at 6 mo., progressive; is now emaciated, big head, does not stand; has had various trials of glandular therapy	Cachectic, irritable; aimless movements of arms and legs; head, 52 cm.; fontanels closed; balances head with difficulty; coarse tremor of hands, cerebellar hypotonia, decubitus ulcer; tap for suprasellar cyst negative	Marked dilatation throughout ventricles; no subarachnoid air; no air in cisterna magna; pontine and interpedencular cisterns not notable; block outside fourth ventricle	32 mo.—Level of 21 mo. to 24 mo.	39 mo.—Level of 24± mo. (Borderline-dull; retardation partly symptomatic) 7½ yr.—Reported arrest of hydrocephalus; improvement in general nutrition; hypotonia remains

of the x-ray findings. The evidence of "cortical atrophy" is undeniable by present standards, the evidence of normal development equally indisputable.

The high incidence of relatively normal development in this selected group of epilepties is not surprising. Of eight cases, only two, or 25 per cent, are mentally defective. In forty-four unselected children with epilepsy studied at this clinic, ranging from 4 to 15 years of age, only 15 per cent were aments; 20 per cent were of borderline intelligence, while 65 per cent were well within the normal range.

It is the pneumoencephalographic findings that require explanation. How can we account for normal development in a child with cortical atrophy?

Two similar cases in young children have been reported in the literature.* Wyatt and Carey[1] describe an infant with congenital neurosyphilis who showed "cortical atrophy" at 6 months of age. She had extensive treatment and developed remarkably well. At 21 months of age her mental development was eighteen months (normal range), and repeat encephalograms showed the ventricles still large but the cerebral sulci of normal depth and width.

Rubin and Rapoport[2] report an infant 20 months of age who had arteriosclerosis and hypertension with a hemiplegic episode, whose encephalogram showed "extensive advanced generalized cortical atrophy." At 22 months of age the maturity level was estimated at 24 months (above average) in spite of a motor and language handicap. The child died shortly after.

Wyatt and Carey's case is of particular importance, because the repeat encephalogram no longer showed any evidence of cortical atrophy. Unfortunately, we have no repeat examinations on any of our cases.

It becomes necessary, at this point, to revise our thinking. Obviously, normal development is possible in the presence of cortical atrophy, so called. The term "cortical atrophy" would seem to be something of a misnomer. The term carries very serious implications, and yet the condition may be only temporary, or even if permanent, without serious effect on cortical functioning. In many instances it is probably nothing more than an indication that intracranial pressure has at some time been increased. It must be assumed that intracranial pressure can be increased for a period, or even repeatedly, without causing per-

*Brines and Lord[3] in a series of cases include two additional children who possibly had cortical atrophy. One infant aged 9 months had recurrent petit mal attacks for six weeks. Encephalograms showed moderately enlarged ventricles and a "moderate excess of air over the periphery." His development was normal. The attacks ceased when the child was 3½ years of age. At 6 years, 1 month of age his I.Q. was 112.

The other child was 3 years and 3 months old; convulsions began at 3 years. Encephalograms showed the lateral and third ventricles to be moderately enlarged, left larger than right, and there was a "moderate amount of air in the subarachnoid spaces." On operation evidence of "an old injury to the arachnoid and shrinking of the convolutions" was found. Convulsions ceased at 4 years of age. At 7 years of age his I.Q. was 117.

manent injury to brain cells, or at least without injuring enough cells to affect cerebral function and development. The effect may be merely to force fluid out of the brain tissue. In other instances, "cortical atrophy" probably represents actual failure of growth of the cerebrum.

Our conclusion is that, *in the presence of normal behavior development*, "cortical atrophy" does not necessarily carry a bad prognosis and may, indeed, be almost without significance.

D. HYDROCEPHALUS

In this group of cases, hydrocephalus is the outstanding clinical feature of the condition, though the etiology, severity, and type of the hydrocephalus vary. Cases 4 and 6 have a communicating form of hydrocephalus; both show "cortical atrophy," and in both cases spontaneous arrest of the hydrocephalus occurred and development is within the normal range. The etiology in Case 4 is obscure; in Case 6 there is an obvious congenital malformation.

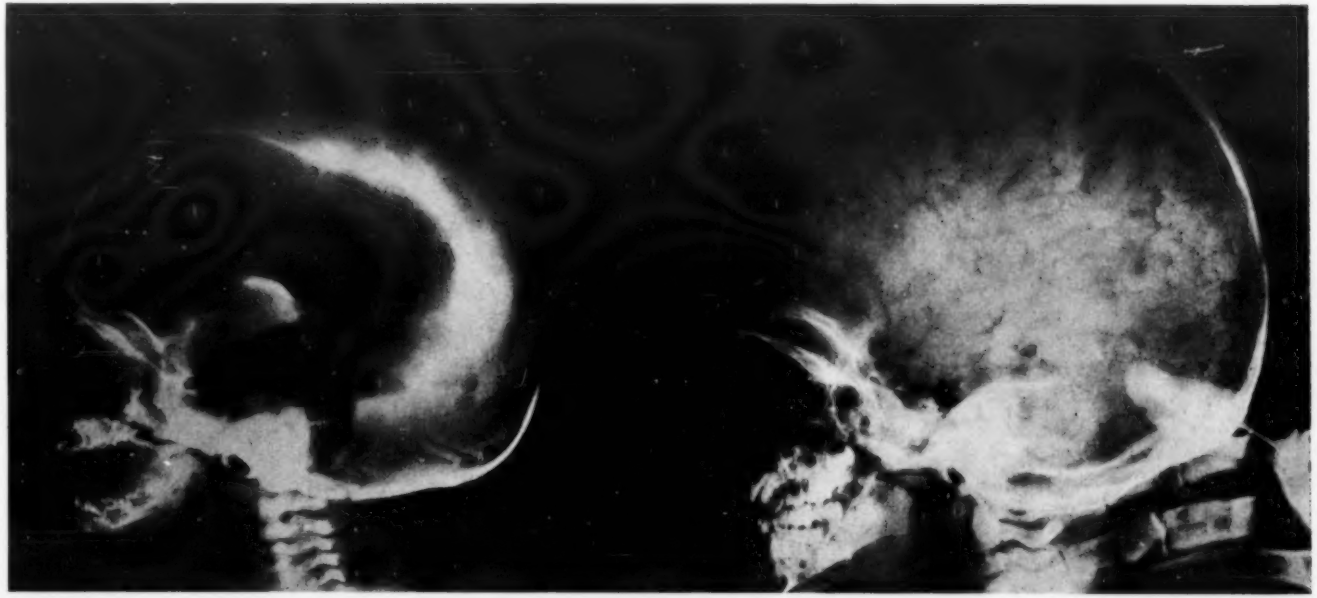
The remaining five cases are obstructive. In three of the infants the choroid plexi were removed in an attempt to reduce the amount of intraventricular fluid; all three were seriously retarded before operation. One died following operation (Case 1), one survived but with no improvement in developmental status; the hydrocephalus continued to progress, and death ensued three years later (Case 3). This child is presumed to have been a primary ament who developed a complicating subarachnoid hemorrhage, followed by hydrocephalus.

In Case 5 an attempt at operative relief was also made; the type of operation is unknown and the child died following operative intervention. Her condition had been progressive, with spastic diplegia and choked discs, though at the time of examination her development had not been greatly affected. The etiology is unknown; it may have been primary (a brother had clubfeet), or it was possibly associated with the birth history, or possibly due to an obscure infection.

Case 7 is equally obscure; the etiology may also possibly be on the basis of birth injury or infection. A suprasellar tumor or cyst was suspected but not found by tap. In this boy the hydrocephalus was associated with anorexia and cachexia; he was completely bedridden and apathetic, and the retardation was probably more a reflection of his listlessness and invalidism than a true retardation. At 7½ years of age the hydrocephalus was arrested and the nutrition improved. He is not considered mentally defective in the crippled children's hospital where he is a patient.

The death rate in the obstructive cases is high (60 per cent). Certainly, the result of operation is disappointing.*

*See Case 3 under "F. Postmeningitis" for a relatively favorable result of operation.



A. *B.*

Fig. 5.—*A*, Case D1, 8 weeks of age. Obstructive hydrocephalus, development grossly defective. Both lateral ventricles are hugely dilated and the third and fourth are greatly dilated. The basal cisterns are not outlined, the sulci unfilled. Obstruction at distal extremity of fourth ventricle. Lacunar skull.

B, Case D6, 30 months of age. Communicating hydrocephalus, development dull-normal. The ventricles are not visualized, but the head size and thin tables indicate hydrocephalus. There is rather marked dilatation of the sulci bilaterally in the frontal region and particularly in the parietal region—cortical atrophy. Note the occipital meningocele under the restraining fingers.

In the communicating cases, the outlook is much more favorable. It is remarkable how well many of these children do from a developmental standpoint, in spite of tremendous ventricular dilatation (and associated cortical atrophy). Among our records is a boy who developed a hydrocephalus following repair of a spina bifida. The hydrocephalus was presumably communicating and it progressed until he was 5 years old, when the head measured 70 cm. He has developed a severe scoliosis with associated spasticity and contractures of the arms and hands in spite of zealous orthopedic care. His development has been followed since the age of 16 months and has always been fully normal. At 7 years he demanded school instruction and is showing normal academic aptitude. No pneumoencephalographic studies have been made on this boy, although the picture can well be imagined; the ventricles would be even larger than those of Case 1!

E. CEREBRAL INJURY

This group includes those children whose original endowment is presumed to have been normal, but who were damaged at birth or in the neonatal period by trauma, hemorrhage, or anoxemia. In all cases under consideration, the damage is considerable and the clinical outlook for normal development was considered very poor before the pneumoencephalogram was made; in this sense we are describing a selected group within this diagnostic classification.

Eight of the ten children are boys. In seven cases the birth history is distinctly abnormal; in seven cases definite disturbances, such as cyanotic attacks, twitchings, inability to nurse, poor cry, and drowsiness, were noted in the neonatal period. All of the children but one show definite evidences of neuromotor damage; six show gross asymmetrical spasticity or athetosis, or both; three show irregular motor incoordinations and tonal disturbances. The one child (Case 8) whose neuromotor system is apparently intact has a definite history of "brain hemorrhage." The one child (Case 9) whose birth and neonatal history were supposedly normal weighed 10 pounds at birth and has a marked bilateral athetosis. He might be considered a congenital athetotic but for the convulsions and deterioration at 18 and 28 months of age which tend to indicate injury. No case had any congenital anomalies; in the eight families with other children, the siblings are all normal, although in Case 10, one child had been stillborn, another had died at the age of 5 days, cause unknown.

This group, then, is characterized by histories of serious difficulty at birth and in the neonatal period, and further by neuromotor disturbances. Convulsions are a common complication. Because of the manner of selecting the cases, all but one (Case 7) are obviously seriously retarded. All infants show gross evidences of abnormality

TABLE V

E. CEREBRAL INJURY

CASE	SEX AGE	CLINICAL HISTORY	PHYSICAL FINDINGS	ENCEPH. EXAM.	DEVELOPMENTAL STATUS	
					EARLY STATUS	FOLLOW-UP
E1	M 36 wk.	First child, normal delivery; cyanotic attack on eighth day; oxygen for 2 days; quiet, weak cry, little activity; minor convulsions began at 5 mo., 2 to 3 daily; poor progress	Fontanels closed, extremities spastic; strong t-n-r.; impassive and impervious	Dilatation of ventricular system; cortical atrophy, right; pachymeningitis, localized	36 wk.—Level of 12 wk. (Imbecile)	
E2	F 40 wk.	One month premature after a fall; birth weight, 5½ pounds; precipitate birth; two attacks of cyanosis and tonic spasms on first day; nursed poorly; respirations irregular; frequent vomiting and cyanotic attacks; poor progress; convulsions at 40 wk. and at irregular intervals subsequently	Nystagmus, blind, neck tense, extremities spastic, reflexes active; fontanels closed at 36 wk.; at times has some light perception	Marked dilatation of ventricles; marked cortical atrophy	12 wk.—Level of 4 wk. 36 wk.—Level of 10 wk.	56 wk.—Level of 8 wk. 2 yr.—Idiot 4 yr.—Idiot
E3	M 44 wk.	First child; labor, 22 hr.; midforceps, feeble cry, very listless, poor color, drowsy, needed frequent stimulation; nursed very poorly; poor progress	Anterior fontanel closed; reflexes very hyperactive, difficulty in grasp (manual coordination); strabismus; mixture of hypotonia and hypertonia	Ventricles within normal limits; cortical atrophy	44 wk.—Level of 24 wk. (Unclassified)	17 mo.—Level of 40 wk. (Unclassified) 4 yr.—Level of 40 to 48 wk. (Idiot)

E4	M 45 wk.	Face presentation, high forceps, reapplied; scars and hematomas on head and ears; resuscitated with difficulty; revived 3 times first day; weak, shrill cry, inactive; jaundice for 5 wk.; poor progress, rigid, tense, abnormal movements, head enlarging	Head circumference, 47.7 cm.; head retracted, back arched, t-n-r, legs scissored; respiratory stridor; extremities spastic, reflexes hyperactive; minimal auditory responses; sees, impassive face, irritable	No visualization of ventricles; marked cerebral atrophy	45 wk.—Level of 20 wk. (Unclassified)	
E5	F 52 wk.	First child, labor induced by quinine; amniotic fluid meconium stained; infant deeply asphyxiated, meconium in throat; nursed poorly, shrill cry, became dehydrated, repeated episodes of apnea with cyanosis first few days; left-sided convulsion at 28 mo.	Internal strabismus; generalized spasticity, more marked on left	No subarachnoid air; dilatation of ventricles	52 wk.—Level of 12 to 16 wk. (Imbecile)	18 mo.—Level of 24 wk. 30 mo.—Level of 12 mo. 45 mo.—Level of 18 mo. 5 yr., 3 mo.—Level of 21 mo. (Imbecile)
E6	M 15 mo.	Second child; labor, 36 hr.; version, forceps extraction after-coming head; normal neonatal period; fair progress?; convulsions began at 13 mo., 2 to 3 daily	Head large, extremities hypotonic; movements somewhat uncoordinated	Dilatation of ventricles; cerebral atrophy	15 mo.—Level of 28 wk. (Unclassified)	25 mo.—Level of 7 to 8 mo. (Imbecile)
E7	M 16 mo.	First child; labor 1 to 2 hr.; difficulty in resuscitation; twitchings noticed at 9 days; does not hold up head, family thinks he understands	Spastic and athetotic; reflexes very hyperactive	Dilatation of ventricles; marked bilateral cortical atrophy; porencephaly right	16 mo.—Gross handicap (?Normal comprehension and interest; unclassified)	24 mo.—Progress in comprehension (Unclassified)

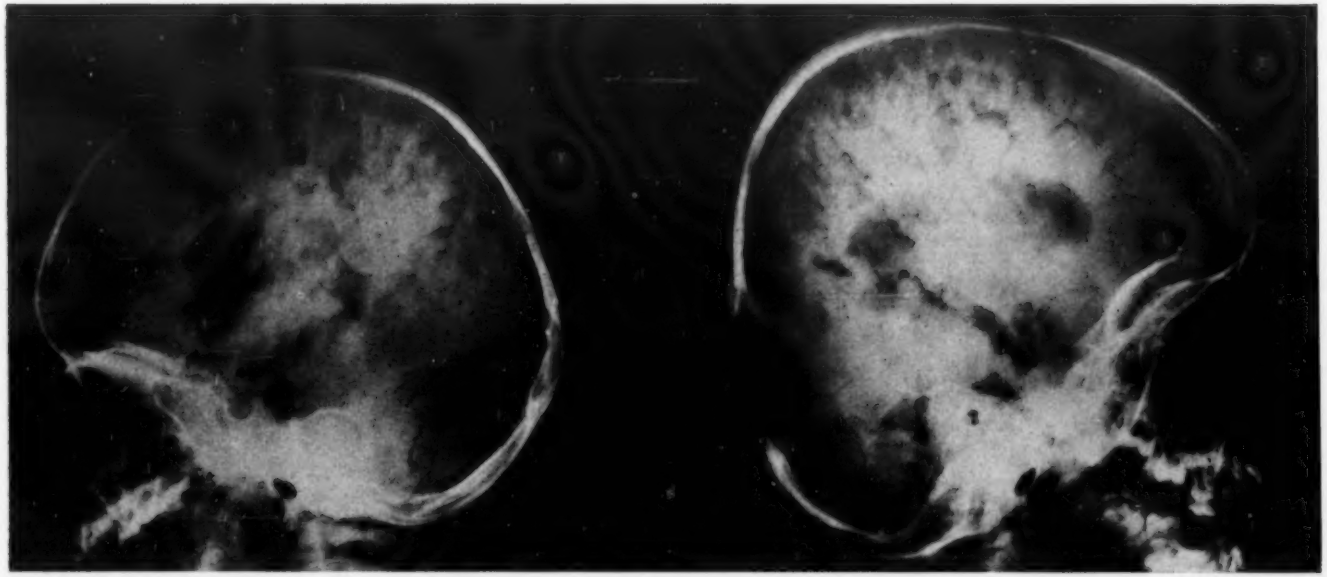
TABLE V—CONT'D

CASE	SEX AGE	CLINICAL HISTORY	PHYSICAL FINDINGS	ENCEPH. EXAM.	DEVELOPMENTAL STATUS	
					EARLY STATUS	FOLLOW-UP
E8	M 22 mo.	Third child; mother had 5 to 6 convulsions before child born; normal delivery but "had brain hemorrhage"; convulsions at 8 mo., 1 to 3 daily to 18 mo.; poor progress	Grossly retarded; fontanels closed; reflexes normal; movements not unusual	Dilatation of ventricular system; unilateral enlargement of left ventricle; generalized cerebral cortical atrophy; porencephaly of left frontal; ?atrophy cerebellum	22 mo.—Level of 20 to 28 wk. (Imbecile)	
E9	M 28 mo.	Birth weight, 10 pounds; second child; seemed normal at birth; neonatal period normal; forceful vomiting frequent since 3 mo.; has always had tremor and strabismus; development slow; severe convulsions at 18 mo.; recurrence at 28 mo.; chronic convulsive state for 9 days	Restless; aimless movements of extremities, blank staring; inconstant tremor of hands; moderate generalized spasticity, reflexes hyperactive, +Babinski	Dilatation of ventricular system; dilatation of basilar cisterns; ?microgyria; ?cortical atrophy left frontal and parietal	15 mo.—Level of 32 to 40 wk. (Athetosis; unclassified) 28 mo.—Level of 40 wk. (Outlook poor)	
E10	M 4 yr.	Labor induced 2 weeks early by quinine, mother preeclamptic; precipitate birth, weight, 7 pounds, 14 ounces; well until third day, when drowsy, blue, refused to nurse; family told had cerebral hemorrhage; vomiting during infancy; did not use left arm until 18 mo. old; convulsions at 2 yr., then frequent twitchings; convulsions at 2½ yr., lost many abilities; "went back to being a baby"	Stands on toes, abnormal gait; does not use left arm well	Dilatation of ventricles; cortical atrophy; porencephaly left frontal	37 mo.—Level of 36 wk. 42 mo.—Level of 40 to 44 wk. (Imbecile)	

TABLE VI

F. POSTMENINGITIS

CASE	SEX AGE	CLINICAL HISTORY	PHYSICAL FINDINGS	ENCEPH. EXAM.	DEVELOPMENTAL STATUS	
					EARLY STATUS	FOLLOW-UP
F1	M 23 wk.	Normal birth; normal progress to 16 wk. when meningococcic meningitis developed; treated with serum; recovery with progressive hydrocephalus and blindness; at 33 wk. and 36 wk. removal choroid plexi with arrest hydrocephalus	At 16 wk., head retracted, back rigid, fontanel bulging and tense, positive Kernig; purulent spinal fluid with meningococci; 25 wk., anterior fontanel 7 × 7 cm.; sutures separated, internal strabismus, hydrocephalic squint; blind	At 26 wk., marked hydrocephalus; no subarachnoid air; ? adhesive arachnoiditis	23 wk.—Level of 12 wk. (Unclassified, blind)	28 wk.—Level of 8 to 12 wk. 38 wk.—Idiot 14 mo.—Idiot
F2	F 25 mo.	Normal birth and development; at 2 yr. acute illness treated with sulfonamide drug for 1 week before hospital admission; stiff neck, vomiting; treated with sulfathiazole; persistent opisthotonus after 2 weeks; slow recovery	Drowsy, pupils sluggish, neck stiff, extremities spastic; spinal fluid purulent, no organisms; 25 mo., slight residual tremor of hands	Dilatation of ventricular system; bilateral cortical atrophy	25 mo.—Level of 21 to 24 mo. (Low average)	30 mo.—Level of 33 mo. (No residuals; high average)
F3	M 6 yr., 10 mo.	Normal birth and development; developmental examination at 42 mo.—level of 42 mo.; at 6 yr., 10 mo., acute illness, drowsy, weakness right side; streptococcic meningitis, prontylin therapy; stormy course with daily ventricular taps, developed enormous left hydrocephalus; 6 yr., 11 mo., operation to reduce small left frontal cerebral hernia; 7 yr., fulguration left choroid plexus; gradual improvement after 2 mo.	At 6 yr., 10 mo., rigid spine, neck painful; right pupil larger than left, weakness right arm and leg; right +Babinski; after 3 weeks choked discs, projectile vomiting	At 7 yr., air in fourth ventricle and cisterna magna, pontine and interpedencular systems; no air in aqueduct, third or lateral ventricles, or subarachnoid spaces; ? block at foramen of Munro, aqueduct of Silvius, and basal subarachnoid spaces	7 yr., 2 mo.—Level of 18 mo. (D. Q. at 20; unclassified)	7 yr., 9 mo.—I.Q., 80 8 yr., 9 mo.—I.Q., 80 9 yr., 4 mo.—I.Q., 88 10 yr., 3 mo.—I.Q., 86 11 yr., 3 mo.—I.Q., 77 (Defect in emotional organization, personality and cerebration; right athetosis)



A. *B.*

Fig. 6.—*A*, Case E7, 16 months of age. Cerebral injury, spastic and athetotic, grossly handicapped and incompetent, excellent attention, interest, and effort. Developmental outlook uncertain. The anterior portions of the lateral ventricles show symmetrical dilatation; basal cisterns are large, the sulci are also quite large—cortical atrophy. There is a collection of air in the frontotemporal region on the right of sufficient dimensions to be called porencephaly.

B, Case E8, 22 months of age. Cerebral injury with convulsions (imbecile). Ventricular system as a whole is enlarged. The very large cisterna magna and enlarged fourth ventricle may indicate cerebellar atrophy. The sulci are markedly widened—cortical atrophy. A rounded area of localized air in the left frontal region is considered to represent a porencephaly.

on pneumoencephalographic examination: localized or generalized cortical atrophy and dilatation of the ventricles are almost universal, and three show evidence of porencephaly. Only two other groups show any incidence of porencephaly. The frequencies are given below:

CLINICAL DIAGNOSIS	NUMBER OF CASES	NUMBER WITH PORENCEPHALY	INCIDENCE PORENCEPHALY (%)
Cerebral injury	10	3	30
Congenital malformations and aplasias	9	2	22
Cerebral degenerative disease	11	1	9

Ford[10] makes a distinction between true porencephaly due to a congenital defect in the brain structure and false porencephaly due to injury or disease, but this distinction cannot always be made with accuracy by pneumoencephalography.

Case No. 7 merits special consideration. The motor involvement is very severe and at 2 years of age this child is quite helpless. He can erect the head only momentarily, cannot sit or roll. All movements are grossly incoordinated and performed only with the greatest difficulty. The facies is normal, handsome, and alert, and he shows a strong desire to stand, to walk, and to watch. Attention is constantly diverted, however, by involuntary head and eye movements. He is able to approach and grasp an object, but he cannot retain it or exploit it in any way. He apparently recognizes many objects by name, he sticks out his tongue to indicate his desire for food, moves his legs to indicate his desire to walk. Interest in the examination procedure is high, and while his performance is almost completely inadequate, it is marked by a very real effort to comply.

The outlook is admittedly very uncertain, and the future depends on his ability to develop some effective means of expression. If he fails in this, he will be virtually handlocked, a prisoner of his disability; development will never have a chance. If he is able to realize on the normal growth potentialities now evident, it will, in all probability, be through the relatively early development of language. This hope is entertained in spite of the pneumoencephalographic findings. The x-ray evidence of cerebral damage is not unexpected; it only corroborates the clinical evidence. And as long as there is clinical evidence of continued developmental progress, it must be given full clinical weight. Repeated developmental appraisals of behavior are necessary in such a case to establish a prognosis.

F. POSTMENINGITIS

This group includes only three children, one of whom (Case 1) was also discussed under "D. Hydrocephalus" as Case 2. In Case 1 the disease was due to the meningococcus; in Case 2, although the spinal

TABLE VII

G. POSTENCEPHALITIS

CASE	SEX AGE	CLINICAL HISTORY	PHYSICAL FINDINGS	ENCEPHAL. EXAM.	DEVELOPMENTAL STATUS	
					EARLY STATUS	FOLLOW-UP
G1	F 21 mo.	Normal birth, normal early development; 40 to 50 words at 15 mo.; walked at 16 mo.; at 17 mo. irritable, loss appetite; ceased walking and talking, sits and sways, grinds teeth; has lost good toilet habits	Tremor of both arms, gross tremor of legs; right pupil slightly larger than left; silly child, peculiar mannerisms	Dilatation ventricles; cortical atrophy	21 mo.—Level of 16 wk. (Idiot)	
G2	F 25 mo.	One of ten children, all normal and stable; patient had developmental examinations at 10 mo., and 18 mo., entirely normal, robust, vigorous child of full, average intelligence, well adjusted; at 19 mo. polioencephalitis with convulsions, coma, flaccid paralysis of right arm and leg with gradual recovery; hyperactive following illness; minor convulsions began at 36 mo. which recur at intervals	Slight atrophy right thigh muscles	7 yr., indeterminate	40 wk.—Average 18 mo.—Average 25 mo.—Level of 21 mo. (Real change in tempo of development and in personality after illness)	30 mo.—Level of 27 mo. 36 mo.—Level of 30+ mo. 5 yr.—I.Q., 80 (Hyperactive; speech defective; postenceph. syndrome; dull normal)

G3	M 29 mo.	Normal birth, weight 8 pounds; early development normal; was creeping and walking with support at 1 yr.; was then sick with "teething" and on recovery could not sit; poor progress since; convulsion at 29 mo., lasting 6 hours; rolls his head	Large head, face imbecilic, emotional; athetosis arms, positive Babinski; positive ankle clonus	Abnormally large third ventricle; left lateral ventricle larger than right; cortical atrophy	29 mo.—Level of 10 to 12 mo. (Imbecile)	
G4	M 33 mo.	Difficult instrumental birth; bright and active in development; walked at 15 mo.; at 18 mo. coincident with "teething," periods of crying and thrashing began; poor development since; cries a lot at night, bangs his head	Negative	Slight dilatation of ventricular system; otherwise indeterminate	33 mo.—Level of 30 wk. (Idiot)	
G5	M 6 yr.	Normal birth; normal development to 10 mo. when had one word plus "mama" and "dada"; could sit alone; at about 1 yr. irritable, "teething"; became seclusive, hyperactive, rocking, little sleep, eats paper and dirt; walked at 17 mo.; does not talk	Active; reflexes hyperactive	Indeterminate	6 yr.—Level of 18 mo.	7 yr.—Level 18 mo. (Idiot)

fluid was grossly purulent, no organisms were found (probably because of sulfonamide therapy before lumbar puncture); in Case 3, the disease was due to the streptococcus. In Case 1 the infant was treated with antimeningococcic serum, and although he survived, he is hydrocephalic, blind, and idiotic. The infant in Case 2 was treated with sulfathiazole and has apparently made a complete recovery without sequelae. In Case 3 the child was treated with prontylin, recovered after a very stormy course, and has a residual athetotic hemiplegia as well as some mental retardation and a defect in emotional organization, personality and cerebration.

The difference in the outcome in the three children is interesting but is not to be ascribed entirely to the difference in treatment. Good and bad results occur under both serum and chemotherapy, although the percentage of complete recoveries is probably higher with the sulfonamide drugs. As significant as the difference in treatment is the difference in age; in Case 1 the infant was only 16 weeks old when stricken.

A reading of Case 1 tells its own story. The other two children need further comment. Case 2 shows x-ray evidence of cortical atrophy in association with normal behavior (see Fig. 7). Again, we must interpret the "atrophy" not as representing destruction of brain cells or arrest of growth of the brain but as a reflection of a recent episode of increased intracranial pressure which is now relieved according to clinical and behavioral signs, and which may well be without adverse prognostic significance.

Case 3 was treated very early in the history of sulfonamide therapy and is believed to be at least one of the first few cases of streptococcus meningitis ever to survive. The course was very stormy, his condition critical for weeks, and the end result, while far from perfect, has far exceeded the wildest expectations of his attending physicians. The athetotic hemiplegia is a crippling motor handicap, but the boy is pleasant, even euphoric, alert, and entirely plausible in his protected home environment. He has a great capacity for rote learning and recites long poems glibly and with great pride. Intellectual and personality residuals are apparent only in such critical situations as mental tests and school. The boy has suffered serious damage, but in view of the history and the known brain changes (which probably include at least unilateral cortical atrophy), his behavioral capacities are truly remarkable.

G. POSTENCEPHALITIS

The infant in Case 2 is the only one in this group in whom the diagnosis of encephalitis was made clinically at the time of illness. This child is of particular interest because she had two previous developmental examinations and was known to be endowed with a robust,

A. *B.*

Fig. 7.—*A*, Case F2, 25 months of age. Postmeningitis, no sequelae normal development. The ventricular system is uniformly and moderately dilated. The cisterna magna is enlarged. The sulci are unduly wide—cortical atrophy.

B, Case G5, 6 years of age. Postencephalitis (imbecile). The ventricles are not unusual, the cisterns appear normal. The sulci are not sufficiently filled to indicate any abnormality. The smoothness of the inner table of the skull at 6 years of age is more suggestive of cortical atrophy than the distribution of air. Findings indeterminate.

vigorous, stable personality and a full, average intelligence. Her progress has been followed for some three years after recovery from polioencephalitis at 19 months of age, and while intelligence has not been greatly affected, there is a perceptible alteration in developmental rate. The most marked change, however, is in the personality field; she is now an overactive, somewhat silly and distractible child with a pronounced speech defect. Petit mal attacks have also developed to complicate the picture.

In the remaining four cases, the diagnosis is only presumptive. It is based on a substantial history of normal development throughout the greater part of infancy, followed by a vague story of a period of malaise, usually ascribed by the family to teething difficulties. The illness was actually considered so trivial that in most cases a physician was not called. On recovery, however, a complete change in behavior gradually became apparent. The outstanding feature of the change is serious mental retardation. It is our impression that encephalitis tends to produce these extreme and devastating changes when it strikes in the first year or two of life. After the second year, the typical sequelae are more apt to be in the personality field (as in Case 2). The older child and adult more typically show the familiar Parkinsonian syndrome when sequelae occur.

The following table correlates the type of sequela with the age of onset of the disease in a slightly larger group of children observed at this clinic.

	NUMBER OF CASES	PROFOUND RETARDATION	PERSONALITY CHANGES	NEUROLOGICAL RESIDUALS*	NO SEQUELAE
Under 2 yr.	13	46%	31%	38%	15%
2 to 11 yr.	8	16%	62%	37%	16%
Total	21	71%			

*No instances of Parkinson's syndrome.

The relationship between the type of deviation and age is well shown.

Of the five children who had pneumoencephalographic studies and whose histories are reported in full, all were under 2 years of age when stricken. Case 1 is the only child who shows no autonomic, emotional, or personality changes (and even she is characterized as "silly"); Case 2 is the only child who does not show gross mental retardation; Case 4 is the only child who shows no residual neurologic signs.

The pneumoencephalographic findings are highly variable. In two children, one of whom is idiotic, no definite abnormalities can be found.

CONCLUSIONS

A series of 53 cases studied by pneumoencephalogram and by developmental examination is reported. The cases are divided and discussed under the diagnostic headings, (A) Congenital Malformations and

Aplasias; (B) Cerebral Degenerative Disease; (C) Epilepsy; (D) Hydrocephalus; (E) Cerebral Injury; (F) Postmeningitis; and (G) Postencephalitis.

The group includes 11 patients in whom development has proceeded normally in spite of indisputable x-ray evidence of cortical atrophy according to present standards: 1 child recovered from meningitis (organism unknown), 2 have a communicating hydrocephalus, 8 are epileptic.

These findings raise a serious question with respect to the role of pneumoencephalography in the diagnosis of cerebral pathology. Pneumoencephalography is, in effect, a major operation and should not be performed when a simpler procedure will do as well or better. The usefulness of pneumoencephalography in many pediatric conditions is not denied, but its limitations need reaffirmation. It is invaluable in the location of intracranial tumors and in establishing the obstructive nature of a given case of hydrocephalus and the location of the obstruction; it is useful in the diagnosis of congenital cerebral malformations. It gives a picture of the anatomy of the brain and establishes an anatomic diagnosis. It does not picture the functional capacity of the cerebrum except when this capacity can be inferred from structural defects, such as tumors, obstructions, and porencephalies. The presence of dilatation of the ventricles and of widened cerebral sulci, or so-called cortical atrophy, does not necessarily indicate any alteration in cerebral function or any diminution in its developmental potentialities.

In pediatric conditions involving developmental factors, it is the developmental examination of behavior status which measures function. To a greater or lesser extent, depending on the complicating factors, it also indicates the future capacities for growth and development. The examination requires training and a special technique but in experienced medical hands it yields highly reliable diagnostic results.

In the presence of normal behavior, pneumoencephalographic evidence of cortical atrophy, so called, is prognostically meaningless, because behavior is the final criterion of the functional integrity of the central nervous system.

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SALICYLATE PROPHYLAXIS IN RHEUMATIC FEVER

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SEVERAL independent studies have shown that rheumatic fever can be prevented if the rheumatic subject is protected from hemolytic streptococcal infection, either by changing his environment or by maintaining a high blood level of sulfanilamide.[1, 2] The former method is not usually practicable for children of the lower economic strata, and the latter method entails possible dangers concomitant with the use of chemotherapeutic agents.[3] Clinical observations on the effectiveness of acetylsalicylic acid in preventing serum sickness[4] and in vitro studies on the interference of antigen-antibody precipitation by salicylates[5] interested us in reinvestigating the application of salicylate prophylaxis to rheumatic children living in the overcrowded tenements of New York City and exposed to the prevalent respiratory infections. The present report is the result of a two-year study.

That the clinical manifestations of rheumatic disease bear a close similarity to those of serum sickness is well recognized. Pathologists have demonstrated that fatal serum sickness in man causes arterial and cardiac lesions with collagen necrosis[6] and sensitization of the rabbit with horse serum produces fibrinoid swelling and rheumatic-like lesions.[7] Of particular interest to the immunologist is the similarity in the evolution of serum sickness and the rheumatic attack. Von Pirquet[8] in his classical studies on serum disease noted the characteristic incubation period between the injection of horse serum and the development of symptoms and proposed the theory that the incubation time is essential for the development of antibodies. Haig-Brown[9] described a similar incubation period between pharyngeal infection and the development of acute rheumatism. Clinical observations, accompanied by studies of the throat flora, have shown that there are three distinct phases in the development of rheumatic fever. Phase I lasts only a few days, during which the patient has an upper respiratory streptococcal infection. This may be so mild that it passes unrecognized. Phase II is the symptom-free incubation period, commonly about ten to fourteen days in duration. Phase III is the rheumatic attack. During the symptom-free interval of phase II there occur immunologic changes which seem closely associated with the development of the rheumatic attack. At the end of phase II there is a diminution in serum complement, suggesting an antigen-antibody reaction.[10] Phase III is accompanied by the appearance of circulating precipitins.[11]

The effectiveness of salicylates in the prevention of the polyarthritis occurring in serum sickness has been demonstrated by Swift and his co-workers.[4] These investigators administered 5 or 6 Gm. of acetylsalicylic acid daily from the beginning of serum therapy for ten days. They showed that the patients so treated failed to develop circulating precipitins to horse serum and escaped arthritis, whereas the untreated patients had a marked rise in precipitins in the circulation with the occurrence of serum sickness. Prompted by these studies, Schlesinger[12] and Sheldon[13]

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tested the prophylactic effect of salicylates on rheumatic children at English convalescent hospitals. Schlesinger administered 2 Gm. of acetylsalicylic acid daily during phases I and II to sixteen children. The drug was continued for one month. No serious recrudescences occurred, although clinically and bacteriologically the infections were similar to those in the untreated group who experienced a high incidence of rheumatic recrudescences. Schlesinger pointed out that two of the sixteen patients had a mild fever and a third had premature contractions about two weeks after infection. Sheldon's results were less favorable; however, this author pointed out that the salicylate dosage may have been too small and emphasized that the use of salicylate in phases I and II is promising.

PROCEDURE

A group of young rheumatic subjects under observation in this clinic were requested to notify us at the onset of pharyngitis. Throat cultures were taken routinely during the fall and early winter months prior to the onset of respiratory infections. On notification, a physical examination was made, salicylate therapy was instituted on patients with pharyngitis, and throat cultures were obtained. If these cultures contained hemolytic streptococcus Group A, prophylaxis was continued for four weeks. The daily dosage was 4 to 6 Gm., depending on the size of the patient. If the cultures contained a respiratory pathogen other than hemolytic streptococcus Group A, salicylates were discontinued and the patients omitted from this study (none of this group developed rheumatic fever). Patients who contracted streptococcal pharyngitis and failed to notify us during phase I were observed as a control group. Blood was taken from each infected patient once or twice a week over a period of two months for determination of the erythrocyte sedimentation rate and the antistreptolysin titer. Two throat cultures were also obtained at least once a month from the other rheumatic subjects in our clinic. All Group A hemolytic streptococci obtained were typed by Griffith's method with certain modifications to be described. The serologic types of infectious agents and the antistreptolysin responses of the salicylate-treated patients were compared with the untreated rheumatic subjects.

RESULTS

The group of forty-seven quiescent rheumatic subjects treated with sodium salicylate following hemolytic streptococcal pharyngitis, escaped clinical manifestations of rheumatic fever with one exception. This 14-year-old colored boy had been instructed to take 5 Gm. of sodium salicylate each day. Three weeks after infection, while presumably taking salicylate, he developed a typical rheumatic attack with polyarthritis and fever and was admitted to the hospital. Two days later he was given the same salicylate dosage with rapid disappearance of symptoms and pyrexia, indicating that he was not refractory to the drug and suggesting the possibility that prophylaxis had not been carried out as advised. Fifteen patients in this group showed a brief asymptomatic

rise in the erythrocyte sedimentation rate within a few days after prophylaxis was discontinued; however, none of these patients developed symptoms or signs of rheumatic activity. Thirty-one patients maintained normal sedimentation rates and likewise escaped both clinical symptoms and signs of rheumatic disease. The untreated control patients behaved in the expected manner; fifty-seven of 139 who contracted pharyngitis developed rheumatic fever. In Table I the contrast in the course of events between the subjects who received salicylates and those who did not is brought out in a conventional contingency table.[14] The value of chi square which the table yields is indicative of overwhelming significance for the differences between the two groups.

Serologic Types of Streptococcus Recovered.—The organisms identified serologically* included nearly all of Griffith's types.[15] Three predominant types were 6, 29, and 30; three types frequently recovered were 2, 12, and 25. These six types were responsible for most of the infections in the treated patients who escaped attacks and also in the untreated controls who developed attacks; that is, the two groups were infected by the same serologic types of Group A *Streptococcus hemolyticus.*

Antistreptolysin Response.—The untreated patients in this series showed the types of antistreptolysin curves which follow hemolytic

TABLE I

THE RELATION OF RHEUMATIC RECRUDESCENSES TO SALICYLATE PROPHYLAXIS

	RHEUMATIC SUBJECTS DEVELOPED RECRUDESCENCES	RHEUMATIC SUBJECTS ESCAPED RECRUDESCENCES	TOTAL
Subjects received salicylates	1	46	47
Subjects received no salicylates	57	82	139
Total	58	128	186

After Yates's correction for continuity, chi square = 21.3.
The value required for significance (P = 0.01) is 6.6.

streptococcal infections. Likewise the patients given prophylactic doses of salicylates developed typical antistreptolysin titer curves; about one-half showed late titer rise similar to that described in rheumatic fever. Sodium salicylate did not modify the antistreptolysin response.

DISCUSSION

One is confronted with the vagaries of rheumatic fever in attempting to evaluate a prophylactic measure. In the cases of salicylate prophylaxis there is the added difficulty of symptoms being masked by the drug. To eliminate this possibility, salicylate prophylaxis was discontinued about four weeks after infection, at a time when rheumatic

*Of 255 strains recovered in 1941, 252 were typed (2 were granular and 1 gave no type). The only change in technique from that previously described[16] was to grow all cultures in 10 per cent carbon dioxide. Many Group A organisms which had not been agglutinated by any of our type-specific sera became typable after eighteen hours' growth in 10 per cent carbon dioxide.

activity might be expected to manifest itself. That the rheumatic process may have been activated briefly during the third week of prophylaxis in fifteen patients is suggested by the erythrocyte sedimentation rate on the withdrawal of salicylates. It is quite clear, however, that with the possible exception of one patient, the development of rheumatic activity was suppressed below the clinical horizon.

Our laboratory has been concerned with investigations of the effect of salicylate on the precipitation of antigen with antibody. The results of these in vitro studies indicate that sodium salicylate prevents antigen-antibody precipitation. This effect is influenced both by the amount of salicylate in the system, increasing with the concentration of drug, and by the proportion of antibody to antigen, decreasing with an excess of antibody and being most marked in the equivalence zone. The mechanism for the interference of immune precipitation by sodium salicylate in vitro appears to be its action on antibody.

SUMMARY

One hundred and eighty-six young rheumatic subjects were observed before and following hemolytic streptococcal pharyngitis.

Forty-seven of this group received prophylactic doses of sodium salicylate. Forty-six escaped and one developed rheumatic fever.

One hundred and thirty-nine patients were untreated. Eighty-two escaped and fifty-seven developed rheumatic fever.

These observations suggest that rheumatic fever can be prevented by the administration of salicylates during the respiratory infection and silent phase.

Statistical treatment of the data indicates that the association between salicylate prophylaxis and the failure of rheumatic subjects to develop attacks following streptococcal pharyngitis is significant.

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BACTERIOLOGIC AND CHEMOTHERAPEUTIC STUDIES IN ACUTE DIARRHEA OF INFANTS AND CHILDREN

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THIS paper reports the bacteriologic and immunologic studies of sixty-three cases of acute diarrhea in infants and young children and the results of therapy with sulfathiazole and sulfaguanidine.

A number of recent articles[1-7] have described the successful treatment of bacillary dysentery with sulfathiazole and sulfaguanidine. Conflicting results have been noted with sulfonamides in the treatment of parenteral diarrhea by some of these authors.

Bacteriologic and immunologic studies of acute diarrhea in infants and children have been made by several investigators.[8-12] These authors have described the relative value of various culture media and the incidence of bacillary dysentery but have made little mention of serum agglutination tests in bacillary dysentery.

MATERIAL AND METHODS

From May to October, 1941, sixty-three cases of acute diarrhea were admitted to the Children's Medical Center. Thirty-nine were under 1 year of age, twenty were between 1 and 2 years, and four between 2 and 5 years. On admission or as soon as possible thereafter, a freshly passed stool was obtained for culture, and for microscopic examination for pus, blood, ova, and parasites. During the child's stay in the hospital an attempt was made to obtain at least three stools for microscopic examination and culture.

Eosin-methylene blue agar, sodium desoxycholate-citrate agar, and SS agar* were used for culture studies. Most of the stools were cultured on eosin-methylene blue agar and SS agar. The usual method of first incubating a portion of the stool in broth for one hour and then transplanting to the plates for twenty-four hours was used. The preliminary incubation in broth was dispensed with when SS agar was used. Suspicious colonies were picked out and transferred to Russell's medium and thence placed in the various sugars for fermentation studies. In many of these cases at least nine plates were streaked out.

Sometime after the tenth hospital day, blood was drawn from the patient for agglutination tests. The tubes were placed in the incubator for two hours and then put in an icebox overnight. An agglutination test was considered positive if the titer was 1:40 or higher.

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BACTERIOLOGIC OBSERVATION

All stools that had a positive Shigella culture had either gross or microscopic pus. Forty-seven cases had pus in their stools. Frequently such stools were preceded or followed by stools during the same day without pus. Unfortunately it was not possible to demonstrate Shigella in all stools containing pus. Twenty-two, or 35 per cent, of sixty-three cases of acute diarrhea had positive stool cultures. Six cases, or 15 per cent, were under 1 year of age and sixteen cases, or 67 per cent, were above 1 year of age. In most instances it was only possible to demonstrate Shigella in one of the three or four stool cultures. The number and type of organisms found were: 9 *Shigella paradysenteriae* Hiss, 4 *S. paradysenteriae* Flexner, 2 *S. paradysenteriae* Strong, 5 *S. paradysenteriae* (unidentified), 1 *Shigella* Shiga. In one case *Salmonella schottmülleri* was found.

At least one agglutination test was made on forty-seven of the sixty-three children with acute diarrhea. Thirty-two, or 70 per cent, were positive in a titer of 1:40 or more. Fifty per cent of the children under 1 year of age and 95 per cent of those over 1 year of age had positive agglutinins for dysentery. There were 4 cases of positive cultures with negative agglutinations. These were a 3-month-old infant with *S. paradysenteriae*, a 4-month-old infant with *S. paradysenteriae* Flexner, a 9-month-old infant with *S. paradysenteriae*, and a 3-year-old child with *S. paradysenteriae* Strong.

There was 1 positive agglutination for *S. dysenteriae* Shiga, 7 for *S. paradysenteriae* Sonne, 15 for *S. paradysenteriae* Hiss, 1 for *S. paradysenteriae* Flexner, 6 for *S. paradysenteriae* dispar, 1 for *S. paradysenteriae* Strong. The case of Salmonella showed agglutinations with paratyphoid B antigen. One patient with a positive Shigella Hiss culture gave a positive agglutination with Shiga. One patient with a positive Shigella Shiga culture gave a positive agglutination with Shigella Hiss. Cases yielding Shigella Hiss cultures had a tendency to give strong agglutinations with Shigella Hiss antiserum and weaker ones with Shigella dispar antiserum. There were no positive cultures for either Shigella dispar or Shigella Sonne organisms, yet there were 7 positive agglutinations for Shigella Sonne and 6 for Shigella dispar.

The results of cultures and agglutinations may be summarized as follows:

12 positive cultures with 12 positive agglutinations
4 positive cultures with 4 negative agglutinations
6 positive cultures with no agglutination tests performed
20 negative cultures with 20 positive agglutinations
11 negative cultures with 11 negative agglutinations
10 negative cultures with no agglutination tests performed.

CLINICAL OBSERVATIONS

Each child who entered the hospital with acute diarrhea was placed in one of three groups. One group received sulfathiazole, one sulfaguanidine, and the third no specific chemotherapy. It was originally intended that these children would be placed in consecutive order into one of the aforementioned groups. Since the morbidity and mortality rates in the summer of 1941 proved to be less severe than in previous years, it was not feasible to do this.

All of the sixty-three infants with acute diarrhea received parenteral fluids, transfusions of blood or plasma, and diet as indicated. For the purpose of determining the effect of chemotherapy, forty-seven cases were classified as bacillary dysentery. The rationale for this classification will be brought out in the discussion.

Sulfathiazole-Treated Cases.—Twenty-three cases were in this group. Sulfathiazole was administered orally in almost all instances. An initial dose of ½ gr. per pound of body weight was given and followed by 1 gr. per pound for each twenty-four hours divided into six equal doses. Sulfathiazole was usually discontinued twenty-four hours after the stools were normal. The blood sulfathiazole levels usually varied from a trace to 13 mg. per cent with an average concentration of 2.6 mg. per cent. No evidence of toxicity, as manifested by skin eruptions, depression of the blood count, or gross hematuria was noted. An occasional dose was vomited.

Many of the children were only moderately ill, but there were several who were desperately ill with fever of 106° F., dehydration, marked toxicity, and convulsions. In all cases the results were very good. The temperature dropped to normal within twenty-four to thirty-six hours, and the toxicity disappeared. The children were alert and active. The stools were of good consistency and normal in number on the average in 5 days. The few instances in which abnormal stools persisted over a longer period of time were complicated by otitis media, pneumonia, or marasmus. Children brought into the hospital twenty-four to forty-eight hours after the onset of diarrhea and who were critically ill gave an excellent response when sulfathiazole was begun immediately. Since such children were often moribund on admission, it was necessary to administer sodium sulfathiazole intravenously.

Sulfaguanidine-Treated Cases.—Sulfaguanidine was administered to thirteen children. The first five received the same dosage as that described for sulfathiazole. The others received an initial dose of ¾ gr. per pound, followed by a maintenance dose of 2½ gr. per pound per twenty-four hours divided into six equal doses. There were no unfavorable reactions. The blood sulfaguanidine level ranged from a trace to 2.25 mg. per cent with the average blood concentration being slightly more than a trace. The course of the disease in this group was quite similar to that of the sulfathiazole-treated cases. Stools were normal in 5.4 days.

As a rule those children entering the hospital with severe complications were given sulfathiazole. However, there were several children who had severe secondary infections who responded well to sulfaguanidine. The concurrent infection improved as the diarrhea ceased.

Results With no Specific Therapy.—There were eleven children in this group. They were only mildly or moderately ill. It did not seem warranted to withhold any therapeutic aid from those children who were desperately ill, because many observers in the past have noted the high mortality rate in this group. Proved cases of dysentery treated in this hospital in previous years were reviewed. The average period of time before stools were normal was 12.5 days, and fever and toxicity were evident for many days, associated with prolonged convalescence. In the present untreated group of moderately ill children, there was a tendency for temperature to remain from about 100 to 101° for several days, and it was necessary to administer parenteral fluids for a longer period of time than in those receiving chemotherapy. Stools were normal on the average in 6.3 days. There were no complications. Several of the children with positive stool cultures were only very slightly ill.

CASE REPORTS

A 9-month-old white female child who had eight to ten loose, green, watery stools for three days entered the hospital severely ill. Temperature was 106° F., and acidosis and dehydration were present. Efforts were made to combat these symptoms with parenteral fluids and blood transfusions. At that time we had not begun the use of either sulfathiazole or sulfaguanidine for bacillary dysentery. Since the child was becoming rapidly worse with high fever, convulsions, and toxicity, it was decided to administer sulfathiazole. This was given parenterally and orally for only fifteen hours before her death. Exitus ensued forty-six hours after admission. Post-mortem examination showed several small ulcers and acute inflammation of the large bowel. Stools obtained before death contained microscopic pus and blood. Cultures of the stools and of the ulcers at post-mortem were negative for dysentery organisms.

Several children who were as severely ill as the child just described have been treated with sulfathiazole and sulfaguanidine. Startlingly excellent responses were obtained in each instance. It seemed to all who saw these children that death would take place, and yet within twenty-four to thirty-six hours the temperature was normal and the child no longer toxic. There were no abnormal stools noted after seventy-two hours.

A 4-month-old moderately acutely ill infant was admitted because of six to eight loose green stools, vomiting, and refusal to nurse for one week. Temperature was 102° F., and there were mild rhinopharyngitis and dehydration. Stools contained pus and mucus. Sulfaguanidine was administered for five days with no improvement in either his general condition or stools. Sulfaguanidine blood level was 1.5 mg. per cent. On the fifth day the temperature rose to 103° F., the child appeared quite toxic and had a moderately severe rhinopharyngitis and otitis media. Sulfathiazole was given with a prompt fall of temperature to normal and

cessation of abnormal stools. The drug was discontinued on the tenth day at which time the child appeared well. On the evening of the thirteenth hospital day the temperature suddenly rose to 105° F., and there was a recurrence of frequent loose stools. Examination was negative, and bacillary dysentery appeared to be the only cause for the child's illness. Accordingly, sulfathiazole was again administered and within thirty-six hours the temperature was 99° F. Stools were normal by the nineteenth day. Stool cultures were negative for bacillary dysentery on the second, fifth, and fourteenth days, but on the sixteenth day *Shigella* Flexner was isolated. On the twentieth day serum agglutinations were negative.

In retrospect it appears that this infant had either a recurrence or a second infection. In both instances, sulfathiazole gave prompt relief. Some observers have noted that occasional cases of bacillary dysentery responded to sulfathiazole after failure with sulfaguanidine. Of interest was the isolation of *Shigella* Flexner while the child had a sulfathiazole blood level of 5.7 mg. per cent and the failure to obtain a positive agglutination reaction.

Nonspecific Diarrhea.—There were 16 cases in this group in which bacillary dysentery could not be proved in spite of complete bacteriologic studies. A number of these were probably dysentery. Thus a set of twins 2 months old, weighing 6 pounds each, entered the hospital with a history of loose, green stools for four to five days. There was a history of recent diarrhea in both parents and several of the older children. Stool examination failed to show pus or blood. Cultures were negative for dysentery organisms, and agglutinations on the tenth hospital day were also negative. These infants were moderately ill. Both were given parenteral fluids. One received sulfathiazole, the other sulfaguanidine. Both made rapid recoveries. Other children with respiratory infections, otitis media, and frequent loose stools who received chemotherapy responded more quickly than did those given the usual symptomatic therapy. Our series is too small, however, to give any statistical data concerning the value of sulfathiazole or sulfaguanidine in parenteral diarrhea.

DISCUSSION

The true incidence of bacillary dysentery in acute diarrhea of infancy and childhood is apparently extremely difficult to arrive at due to geographical differences, seasonal variations in morbidity and mortality rates, methods of culture, and age of patients.

The pediatric literature on diarrhea reveals much confusion which is partly due to indiscriminate usage of the term dysentery. Dysentery has been used by some writers to include bacillary or amebic dysentery, infectious diarrhea, and parenteral diarrhea. Others use the term correctly and include only diarrhea due to dysentery organisms or to *Endamoeba histolytica*. Acute diarrhea appears to be the most appropriate terminology when the etiology is unknown.

The incidence of bacillary dysentery in acute diarrhea of children has been determined by a number of investigators. Cooper, Furcolow,

Mitchell, and Cullen[12] found 49 per cent of their cases had dysentery; Kemp and Haberman,[10] 43 per cent; Haynes,[9] 45 per cent. In this study 35 per cent of the sixty-three patients with acute diarrhea had positive stool cultures. The only criterion in each instance was a stool containing dysentery organisms. However, if only the forty-seven cases with pus in the stools were included, the incidence of positive stool cultures in this series would be 47 per cent.

The number of positive cases increased when a greater number of stool cultures were made. Cooper and his co-workers in 1939 investigated several media and found that sodium desoxycholate citrate was superior to other media. However, in 1941, these authors reported that SS agar gave the best results. We did not make as extensive a study of different media as did Cooper, but it is our impression that SS agar is superior for isolating dysentery organisms. Cultures obtained at proctoscopy apparently produced no appreciable increase in the number of positive cultures since Haynes found an incidence of only 45 per cent. Moreover, this method is time consuming and not unattended by some danger.

The history, clinical course, and autopsy findings often are very characteristic of bacillary dysentery, but the stool cultures are negative. Thus the death which occurred in our series had negative ante- and postmortem cultures.

It has seemed to us that because there were so many variable factors in determining the incidence of dysentery, more than the single criterion of a positive stool culture should be considered. We have used the following rules in classifying a case of acute diarrhea as dysentery in infants and young children:

1. Positive stool culture for bacillary dysentery.
2. Positive serum agglutination of 1:40 or more.
3. Gross or microscopic pus and blood in the stool. A microscopic examination determined the presence of ova or parasites. Ten to fifteen leucocytes per high power field were considered significant, since few other conditions produced pus. A family history of diarrhea together with hyperpyrexia, convulsions, toxicity, and dehydration, and frequent abnormal stools were considered very suggestive of dysentery.

From a therapeutic point of view, a microscopic examination of the stool together with the clinical picture leads to a working diagnosis and allows specific therapy to be instituted at once.

Using this classification, forty-seven cases of dysentery were found in sixty-three patients with acute diarrhea. Only two cases of the forty-seven had no pus in the stools. Both cases had negative stool cultures but had agglutination tests for *S. paradysenteriae* Sonne in titers of 1:80 and 1:160. Five cases were included in the dysentery group that had negative cultures and no agglutination tests were done. In each instance the character of the stools and the clinical course were very suggestive of

dysentery. One of the five cases had a positive stool culture for *Bacillus alcalescens*, but since the pathogenicity of this organism is in doubt we have called it a negative culture for dysentery.

There is apparently no agreement as to what constitutes a diagnostic agglutination reaction. Cases of dysentery with positive stools may have negative agglutinations or positive agglutinations with a titer of only 1:40 (Nelson,[8] Smith, and Fraser[13]). Studies by Felsen and Osofsky[14] and Smith and Fraser,[13] in which they did agglutination tests for dysentery on apparently healthy adults, showed that 26 and 24 per cent, respectively, were positive. Felson and Osofsky thought these individuals had dysentery without ever having been aware of it. Mackie,[15] however, believed that the agglutination reaction of the patient's serum unsupported by confirmatory bacteriologic evidence did not constitute valid proof of *S. paradysenteriae* Flexner or Sonne, since he felt there was a close antigenic relationship between these organisms and *Escherichia coli*. Blatt and Shaw[11] point out that from their study of bacillary dysentery in children the serum agglutination reaction was dependable. They stated that "one criticism of the test is that the patient's serum often agglutinates more than one type of dysentery bacilli. This cross agglutination is due to the similarity of the somatic antigens in some of the dysentery bacilli. However, the causative type is usually agglutinated to a higher dilution than the other types." It is to be noted that Mackie studied only adults.

To our knowledge, no extensive series exists in which agglutinations were done on healthy infants and children. This seems to be the crux of the problem, for it appears that in infants and young children dysentery antibodies are not found with as great a frequency as in adults. In four children in whom we found positive cultures for dysentery organisms and negative agglutinations, three were under 9 months of age.

Zinsner and Jones[16] in their textbook stated that a titer of 1:50 is significant. Fothergill[17] believed 1:40 indicated dysentery. Haynes[9] considered 1:80 or higher to be of value in confirming the diagnosis of dysentery. In our series only six cases had a titer of 1:40. The highest titer was 1:640 with *S. paradysenteriae* dispar in a child with negative stool cultures. The highest titer was usually obtained the third week after the onset of the disease.

Cross agglutinations were frequently noted. Hiss organisms often gave a high titer for Shigella Hiss and a lower one for Shigella dispar. The value of agglutination studies was shown by finding seven positive agglutinations for Shigella Sonne and six for Shigella dispar in patients with negative cultures. We have considered a titer of 1:40 to be positive for dysentery.

Uniformly excellent results were obtained with sulfathiazole or sulfaguanidine in those cases designated as dysentery on the basis of our

classification. This is in accord with the reports of Marshall, Lyons, Anderson, Taylor, Cooper, and others. However, if only the 22 cases with positive stool cultures are considered, the results seem to be equally good. Thus 9 cases treated with sulfathiazole had normal stools on the average in 4 days, 9 cases treated with sulfaguanidine had normal stools in 5.8 days, and 4 cases that received no chemotherapy had normal stools in 7 days. No toxic effects were noted with either sulfathiazole or sulfaguanidine. Most of our patients came from a very low economic and social level. These children usually had such complications of acute diarrhea as severe upper respiratory infections, otitis media, and pyodermia. Sulfathiazole appeared more effective in these children. Anderson and Taylor have reported good results with sulfathiazole in parenteral diarrhea, but Cooper[5] has not found it effective. It seemed to hasten recovery in our series. This might probably be due to its effect on the parenteral infection. Sulfathiazole appears to us to be the drug of choice because it has been used here in many hundreds of cases with few ill effects, while our experience with sulfaguanidine has been limited. Moreover, sulfathiazole can be administered parenterally.

Chemotherapy appears to be more effective when instituted early in the disease. Nevertheless, in some cases in which drug therapy was begun late in the course of the disease, there was a prompt cessation of abnormal stools and drop in temperature to normal within twenty-four to thirty-six hours. These cases, however, might have had a similar course without therapy.

SUMMARY

Sixty-three cases of acute diarrhea in infants and children were studied. Several media were used for stool cultures. SS agar appeared to give the best results.

Twenty-two cases, or 35 per cent, had positive stool cultures indicating acute bacillary dysentery. Fifteen per cent of the cases under 1 year of age and 67 per cent over 1 year had positive stool cultures.

Agglutination tests were performed on the sera of forty-seven patients. Thirty-two, or 70 per cent, were positive in a titer of 1:40 or more. Fifty per cent of the cases under 1 year of age and 95 per cent over 1 year had positive agglutinations.

All stool cultures positive for bacillary dysentery contained pus. There were two cases with positive agglutinations in high titers that did not have pus in their stools.

Sulfathiazole and sulfaguanidine produced marked improvement. There were an immediate drop in temperature, a rapid loss of toxicity, and normal stools in about five days. No untoward reactions were noted with either drug. Sulfathiazole appeared to give better results by bringing about speedier recovery, especially in those infants with severe secondary infections. Moreover, it proved to be effective in those cases

which failed to respond with sulfaguanidine. Sulfathiazole has the added advantage in that it can be given parenterally to the very severely ill child who is either moribund or vomiting.

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GASTROINTESTINAL ALLERGY AND THE CELIAC SYNDROME

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IT IS now generally conceded that celiac disease is not a disease entity but a clinical syndrome[1] characterized principally by the elimination of large, pale, frequently frothy, offensive-smelling stools containing a large amount of fat and abdominal distention, wasting, and stunting of growth. The latter is dependent upon the severity and the duration of the underlying pathologic process. Deficiency symptoms may or may not be present. It is also recognized that the underlying etiology and pathology may vary in different cases. Thus the celiac syndrome has been frequently classified as follows:

1. The type involving cystic fibrosis of the pancreas with steatorrhea (probably congenital and usually fatal).
2. The type arising secondary to gastrointestinal diseases (dysentery, tuberculosis, parasitic disease, etc.).
3. The so-called idiopathic type (now considered to be the usual celiac disease; usually responds satisfactorily to proper dietary management).

To the above classification I believe that we are justified in adding a fourth group, namely, *the celiac syndrome resulting from gastrointestinal allergy*. It has been my experience in the last two years to observe three cases of the celiac syndrome which gave every evidence of resulting from food allergy. These cases fitted so well into the picture of what we usually consider typical celiac disease that a description of them should be of clinical interest. At the same time it is the purpose of this paper to suggest that simple clinical observations may establish the etiologic diagnosis in this particular form of the celiac syndrome so that detailed laboratory procedures may not be necessary.

CASE REPORTS

CASE 1.—S. K., male, 19 months of age, full-term, normal delivery; birth weight, 7 pounds, 4 ounces. Only child; no previous illness. Family history reveals mother and maternal aunt have pollinosis.

The infant was breast fed exclusively up to 4 months of age, at which time a formula of diluted cow's milk and sugar was prescribed. Cereal had been added at 3 months of age and was well tolerated. At 5 months, following the ingestion of a vegetable soup mixture, he developed a mild papular eruption. The soup mixture was discontinued, and, after trial and error, it was found that he was able to tolerate certain individual vegetables. He continued to do well until 1 year of age, when he developed a diarrhea, which continued for three days, and was followed by a maculopapular skin eruption. There was a watery, mucoid discharge from the nose. He was placed on a diet of boiled, skimmed milk, ripe bananas, and scraped apple, and the diarrhea stopped for a few days. Attempts to add various foods to the diet caused a flare-up of the diarrhea. At 16 months of age he was having

four to seven foul-smelling, grayish green, mushy stools daily, with a great deal of abdominal distention in spite of a diet consisting of boiled, skimmed milk with casec, ripe bananas, lean beef, lamb, cottage cheese (from skimmed milk), and jello. Cereals, citrus fruits, and all vegetables were eliminated from his diet with no improvement. The diet was supplemented by vitamin concentrates. Between the ages of 1 year and 17 months he lost 4 pounds, his abdomen became greatly distended, he was irritable, his appetite became poor, his color was pale and sallow. Because of the persistent diarrhea and loss of weight, he was hospitalized at the age of 17 months.

At this time, he had the typical appearance of a child with celiac disease. Culture of the stools gave negative results for pathogenic microorganisms and parasites. The blood agglutination tests were negative. Stools contained an increased amount of fat. He was skin tested with the following results: positive cutaneous reaction to rye, barley, corn, orange, asparagus, and plum. Wheat, milk, and eggs were negative. Intracutaneous tests to milk, wheat, and eggs were negative. Blood examination revealed no significant changes.

While in the hospital, he refused powdered protein milk and took only ripe, mashed bananas, meat, and jello, whereupon he became constipated for the first time in several months. On returning home, he had a recurrence of the diarrhea when boiled skimmed milk was added to his diet. Cow's milk has been discontinued, and at the present age of 19 months he is having normal bowel movements on a diet consisting of soybean milk, meat, bananas, rice, string beans, and peas. He is unable to take citrus fruits and certain vegetables. His diet is supplemented with ascorbic acid, vitamin B complex, and a vitamin A and D preparation. In the past month his abdominal distention has receded; he has gained five pounds, is happy, and has a good color.

CASE 2.—R. A., male, 4 years of age, full-term, normal delivery; birth weight, 7 pounds, 4 ounces. Male sibling, 6 years of age, in good health. Developmental history normal except for slow eruption of the teeth. Family history negative for allergy.

He was in good health until 1 year of age, at which time he developed a diarrhea characterized by frequent, watery to mushy, light gray to green, foul-smelling stools, usually two or three during the night and as many as five or six during the day. The abdomen became distended, and there was a gradual loss of weight. At 13 months of age he was placed on a diet composed of boiled skimmed milk, cottage cheese (from skimmed milk), eggs, beef, ripe bananas, scraped apple, ascorbic acid, and vitamin A and D concentrate. In spite of this diet and medications of bismuth, camphorated tincture of opium, the stools continued three to four in twenty-four hours, mushy in consistency and foul smelling, accompanied by a great deal of flatus and abdominal distention.

At 17 months of age, five months after the onset, there was little improvement although the diet had been altered at various times. The child had lost two pounds in weight, had become irritable and pale, and his muscle tone was poor. For one week on a diet of powdered protein milk, cottage cheese, and ripe bananas, his stools diminished to three daily, but they were not formed. At 18 months of age cow's milk was removed from the diet on the possibility that it was not agreeing with him, and within forty-eight hours he showed marked improvement. The stools decreased to two daily, were well formed, and became normal in appearance and color within one week. Within two weeks the child was doing well on a diet consisting of puréed vegetables, cooked cereal, ripe bananas, meat, jello, and eggs. The addition of orange juice brought about a temporary flare-up. At 20 months of age he was given evaporated goat's milk and tolerated the addition well. At 2 years of age he was given a small amount of cow's milk and suffered a return of the diarrhea and an eczematoid eruption

in the cubital fossae. During the past two years he has remained well, continues to gain weight, and has normal bowel movements on a liberal diet that contains goat's milk but no citrus fruits. Desensitization with cow's milk is being contemplated.

On one occasion, his stools were cultured for pathogenic organisms and found to be negative. Twice during the diarrheal episodes, the stools were found to contain an excess amount of fat. The type was not determined.

CASE 3.—R. A., female, 3½ years of age, spontaneous, normal delivery; birth weight, 8 pounds. Only child. Family history of allergy.

During the first month the infant had a seborrheic dermatitis of the scalp. Progress was good until 15 months of age, when she developed a diarrhea consisting of foul-smelling and greenish stools containing incompletely digested food. At the same time there developed an eczema of both cubital fossae. Diarrhea continued for the next three weeks, four to five times daily, on a diet consisting of boiled skimmed milk, cottage cheese (from skimmed milk), beef, ripe bananas, scraped apple, hard-boiled egg white, and jello. No improvement was effected by substituting protein milk for boiled skimmed milk. At 17 months she was still doing poorly on the restricted diet; she had lost four pounds; the abdomen was markedly distended; she was nervous and irritable and the eczema persisted.

At 18 months of age cow's milk was eliminated from the diet, and there was immediate improvement, including disappearance of the eczema. Cutaneous tests revealed orange juice and wheat positive; intradermal tests revealed wheat positive, milk and eggs negative. Milk, wheat, and all citrus fruits were permanently eliminated from the diet. She was last seen at 3½ years of age and has been well during the past two years except for minor upper respiratory infections. All milk, wheat, and citrus fruits are still eliminated from the diet. Various attempts to add any of these foods have met with either diarrheal episodes or eczema. During the diarrheal episodes her stools were cultured on two occasions, and no pathogenic organisms or parasites were found. Simple macroscopic tests for fat in stools revealed increased amount during the most severe diarrheal episodes.

DISCUSSION

These three patients all have one syndrome in common: chronic diarrhea consisting of foul-smelling, large stools, with an increased amount of fat, abdominal distention, loss of weight, irritability, and anorexia. In two infants, Cases 1 and 3, there was a family history of allergy. In addition, the patients in Cases 1 and 3 had other manifestations of allergy; rhinorrhea and eczema in one (Case 1), and eczema in the other (Case 3). All three of the infants had multiple food allergy, as evidenced by either "trial and error" methods or skin testing; all were unable to tolerate cow's milk, which apparently was the most serious offender, since elimination of cow's milk from the diet resulted in a cessation of the diarrhea in all three patients.

It is not the purpose of this paper to discuss in detail the etiology and pathology of the celiac syndrome. For such discussion the reader is referred to the paramount work of Andersen,[1] Rauch, Litvak, and Steiner[6] and others who have shown that the underlying pathologic anatomy and physiology of certain severe forms of the celiac syndrome is cystic fibrosis of the pancreas and have thoroughly discussed the differentiation of this process from so-called typical celiac disease. So

much has been concerned with the differentiation of cystic fibrosis of the pancreas from idiopathic celiac disease by virtue of history, response to treatment, and especially elaborate diagnostic laboratory procedures (including chemical analysis of the stools for fat partition, vitamin A absorption, dextrose tolerance, duodenal aspiration for pancreatic enzymes, and blood enzyme determination), that little consideration has been given to simple clinical observations relative to the celiac syndrome that are important in eliminating milder forms before detailed studies become necessary.

It is also not the purpose of this paper to discuss the value of these various diagnostic procedures, which cannot be underestimated in intractable cases of the celiac syndrome. However, we must realize that this condition may become intractable if there is failure to recognize simple etiologic factors such as presented in these case reports and in such instances even the detailed laboratory tests previously mentioned probably would be of little significance. It is interesting that the condition of the two patients (Cases 1 and 3) had been diagnosed as celiac disease by other physicians and were treated as such with unsatisfactory results. It is also significant that allergy was suspected as a possible underlying factor in both of these patients, but following negative cutaneous and intracutaneous tests to milk, the probability of milk allergy was not considered seriously and milk was not eliminated from the diet early in the course of the disease. This brings up the important question of the value of skin testing in infants, and it is believed by many that in young individuals results are not significant, inasmuch as positive tests are found in infants who present no clinical allergic manifestations, and negative tests are found in infants who are highly allergic to the particular allergens.

A survey on modern treatises on pediatrics[2, 4] and allergy[3, 8, 9] reveals little in regard to chronic diarrhea in infancy and childhood resulting from gastrointestinal allergy, although acute disturbances, such as pylorospasm, vomiting, colic, and various symptoms simulating organic disease, are frequently mentioned.

Rowe's[5] work on food allergy is outstanding, and he in particular has emphasized the importance of food allergy in gastrointestinal disturbances of infancy and childhood. "Several patients with long-standing diarrhea, weakness, and other symptoms, formerly diagnosed as due to irritable bowel, have been relieved by persistent use of diet manipulation according to my elimination methods. Milk especially was culpable in two patients." Tallerman[7] found many patients with gastroenteritis suffering from milk allergy, and Pounders[7] reports chronic diarrhea in infants resulting from milk allergy. Others refer briefly to diarrhea resulting from food allergy.

For a discussion of the pathologic physiology of gastrointestinal allergy, the reader is referred to the works of Rowe, Schloss, Ratner, and others.

CONCLUSIONS

Gastrointestinal allergy should always be considered as an etiologic possibility for chronic diarrhea, with or without the celiac syndrome, particularly when there is a family history of allergy and when idiosyncrasies to individual foods, such as vomiting, abdominal pain, eczema, nasal discharge, coughing, etc., are revealed by a careful history.

On the basis of the observations made on these three patients, it is suggested that all patients suspected of having celiac disease and who do not respond favorably to the "celiac diet" in a reasonable length of time, should be given a diet from which milk has been removed (as well as other possible allergens) before further elaborate diagnostic procedures are instituted. In addition, a careful family history for allergy and a detailed history of the infants' reactions to various additions to the diet should be sought as added evidence. In the event that elimination of milk and possibly other foods does not result in improvement, then further diagnostic procedures can be contemplated, namely, analysis of the fat content of the stools, glucose tolerance, possibly vitamin A absorption, and also enzyme determinations of the duodenal contents. Skin testing apparently is inconclusive in the diagnosis of food allergy in infancy.

SUMMARY

1. Three cases of gastrointestinal allergy presenting the "celiac syndrome" are reported.

2. In all instances, evidence is presented that cow's milk was the principal offending food.

3. It is suggested that food allergy be considered as a possible cause for the celiac syndrome.

4. It is recommended that milk and other foods be eliminated individually from the diet of all infants presenting the celiac syndrome as a diagnostic and therapeutic procedure before elaborate diagnostic tests are resorted to.

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104 S. MICHIGAN AVENUE

TREATMENT OF INFLUENZAL MENINGITIS WITH ANTI-INFLUENZAL RABBIT SERUM AND SULFAPYRIDINE

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THE mortality of influenzal meningitis, prior to the introduction of sulfonamide therapy, fluctuated between 90 and 100 per cent. Use of the sulfonamides has measurably reduced the death rate, and a combination of these drugs with anti-influenzal rabbit sera has achieved the best results to date. During the year ending Sept. 1, 1941, nine patients suffering with influenzal meningitis were admitted to the Children's Hospital of Pittsburgh. Five of these nine cases recovered completely. All were treated with type B anti-influenzal rabbit serum and a sulfonamide drug. Some received in addition the sodium salt of hydroxyethylapocupreine hydrochloride (designated B71 for brevity) intrathecally. Details of therapy in these patients will be discussed later.

It is not easy to evaluate the efficacy of the various sulfonamides already used in influenzal meningitis because of the difficulty of obtaining for summarization an accurate and complete list of the many singly published cases in which drug therapy was employed. Furthermore, in many of the treatments the drug has been supplemented by serum. A review of the recent mortality rates following the use of sulfanilamide in influenzal meningitis is given by Sappington and Favorite[1] who also report two patients treated unsuccessfully with this drug. Alexander,[2] analyzing records gleaned from the literature, of 52 patients treated with sulfanilamide, found a mortality of 80 per cent. Applebaum[3] had one recovery in 18 treated patients. Aleman[4] collected data on 82 patients treated with sulfanilamide and listed recoveries in only 10.

Better results have generally been reported with sulfapyridine, although Aleman[4] treated 8 patients with no recoveries. Arnett, Shoup, and Henry,[5] analyzing various published reports of the use of sulfonamide drugs, found 14 recoveries in 25 patients treated with sulfapyridine. Neal, Applebaum, and Jackson[6] obtained four recoveries in eight children treated with sulfapyridine, its sodium salt, or both. The actual mortality rate with these drugs is probably higher than that indicated by the above figures, because many single fatal cases have not been reported.

At the time the first of our patients was admitted, no reports were forthcoming in the literature regarding the use of sulfathiazole in influenzal meningitis. Animal experiment has shown that the drug was poorly concentrated in the spinal fluid when given by the oral or intravenous routes. Recent studies indicate that this drug may be less efficient than other more diffusible sulfonamides.

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Treatment with antiserum falls into two groups, depending upon whether the serum is obtained from horse or rabbit. Use of antiinfluenzal horse serum was reported by Ward and Wright[7] in 8 children suffering with influenzal meningitis with one recovery. Ward and Fothergill[8] treated 5 patients with serum reinforced with complement but none recovered. The bacteriostatic effect was seen in the temporary sterilization of the cerebrospinal fluid and the formation of circumscribed abscesses in the arachnoid spaces. Fothergill and Wright[9] reported 10 recoveries and 26 deaths in patients treated with horse serum. Fothergill[10] later in a survey of the results obtained with serum treatment in 201 patients in various clinics recorded a mortality of 84.6 per cent. Pittman,[11] using antiserum from horses immunized against *Hemophilus influenzae,* type B, obtained 1 recovery in 18 patients. Only 13 of these meningitides were due to the type B strain. More favorable results were achieved by Silverthorne, Frazer, and Snelling[12] who treated 36 patients with 10 recoveries. Silverthorne and Brown[13] obtained 15 recoveries in 65 patients by the use of antiserum supplemented by rabbit, horse, guinea pig, or human complement in combination with sulfonamides. Lindsay, Rice, and Selinger[14] reporting 108 patients, listed a mortality of 83 per cent when Fothergill's serum supplemented with human complement was used intrathecally along with transfusion. More significant was the reduction to a 54 per cent morality rate in 13 children treated with a combination of antiserum and sulfonamides.

Alexander,[2] profiting by the earlier studies of Pittman[15] on the separation and identification of a meningitic strain of *H. influenzae* and by the fact noted by Pittman and Goodner[16] that complement fixation of purified specific carbohydrate of this organism takes place in rabbit but not horse serum, used the B strain to prepare a specific rabbit antiserum. The smaller size of the protein molecule of the rabbit antiserum also probably enhances its diffusibility. Alexander[2] reported 17 recoveries and 11 deaths, a mortality of 40 per cent, following the use of specific rabbit antiserum supplemented with sulfanilamide or sulfapyridine. Recently Dingle and Finland[17] cite a personal communication from Trask, who obtained "14 recoveries among 15 consecutive patients with influenzal meningitis treated in accordance with Dr. H. E. Alexander's recommendations."

Between 1930 and 1937, a period prior to the introduction of the sulfonamides, 33 patients suffering with meningitis and from whose spinal fluid *H. influenzae* were cultured were admitted to this hospital. Only 1 of these, a white female aged 4 years, recovered. This child who had a spinal fluid cell count of 2,100 on admission was treated with salol and discharged after sixty-six days. Between the years 1937 and 1940 there were 14 patients treated with sulfonamides and Fothergill's horse serum. One of these, with an initial spinal fluid count of 3,800 cells, recovered. A sulfapyridine dosage of 90 gr. daily for three days resulted

in a spinal fluid concentration of the drug of 8.8 mg. per cent. The total daily dosage averaged 23 gr. for twelve days.

In the 9 cases of influenzal meningitis discussed in this paper, *H. influenzae* were recovered from the spinal fluid in stained smear and culture. All were proved to belong to strain B by capsule swelling in specific antiserum. Squibb's anti-influenzal rabbit serum combined with one or more sulfonamides was used in treatment. In 5 cases B71 was also used. Progress of treatment was checked by cerebrospinal fluid cell count and temperature fluctuations and by testing homologous organisms against the patient's cerebrospinal fluid or blood serum for capsular swelling. The B71 was used intrathecally in 2 to 10 c.c. doses of a dilution of 1:1,000, a concentration that could be safely given intrathecally, because it was felt that this drug might have some sterilizing effect on the cerebrospinal fluid. This chemical had previously been used in the treatment of pneumonia with considerable success at the Children's Hospital in Pittsburgh.[18, 19] The pertinent clinical data pertaining to the patients are tabulated in Table I. The details of the therapy with antisera and sulfapyridine are summarized in Table II. Two of the patients who died, J. H. and N. L., received sulfathiazole as well, and two of the patients who recovered, V. B. and O. F., received sulfanilamide in addition.

The initial erythrocyte count varied between 3.7 and 4.1 millions and the hemoglobin values between 8 and 13.6 Gm. per 100 c.c. In three of the fatal cases the initial hemoglobin was between 8 and 9 Gm. per 100 c.c. Both hemoglobin and erythrocytes were proportionately depressed during sulfapyridine therapy. Such losses were controlled by transfusion. White blood cell counts on admission varied from 5,000 to 29,000. No serious leucopenia developed under intensive therapy. Tendency toward leucopenia was readily combated by transfusion.

The outstanding conditions which militate against favorable outcome to treatment are undoubtedly the severity and the duration of the infection. An initial high cerebrospinal fluid cell count gave a grave prognosis except perhaps in older children. Age was a less significant factor in prognosis in our cases, although one of the four fatal cases was 5 months old. Only one of the fatal cases lived over four days and death in this patient was due to drug nephritis and not to the meningitis. An associated mastoiditis which was present in five of our patients prejudices unfavorably the patient's chance of recovery and especially if operation is delayed. In many of the patients with otitis the membrana tympani appeared normal or only slightly inflamed with no bulging. Definite diagnosis was difficult. The lack of early signs in antrum or mastoids, where subsequently positive evidence was found, may have been due to the fact that the otologist usually saw these cases after serum therapy had been instituted. In our experience a myringotomy has occasionally yielded only blood. This procedure may be misleading unless

careful culture technique is carried out.[20] Occasionally negative cultures have been obtained in patients with involvement of the antrum. Mastoiditis, not shown by x-ray, was revealed by post-mortem examination in the only patient where necropsy permission was obtained. In one of the four fatal cases (N. L.) death was due to a nephritis caused by the sulfonamides employed in treatment rather than to the infection. In addition to intravenous sodium sulfapyridine used in the first three days of treatment, a total of 2,564 gr. of sulfathiazole was given orally for the twenty-two hospital days. The average number of grains per day was 115. The recurrence of organisms in the spinal fluid of this patient on the eighth hospital day prompted an increase in the sulfathiazole dosage from 80 to 160 gr. daily. This increased dosage was followed by marked improvement lasting for six days. The patient died on the twenty-second day from a nephritis undoubtedly related to drug. Two days prior to death the spinal fluid was sterile and contained only 3 white blood cells and a trace of globulin. The highest concentration of the cerebrospinal fluid was 3.1 mg. per cent, the lowest 0.9, and the average 1.5. One other patient, J. H., received one dose of 40 gr. of sulfathiazole in addition to 220 gr. of sulfapyridine in thirty-six hours. This child was in extremis on admission and the large dosage of sulfapyridine was given in a futile attempt to modify the course of the infection. Post-mortem effects of the drug treatment appeared to be limited to extensive fatty degeneration and fatty infiltration of the liver, and acute hepatitis. The leptomeninges were infiltrated with an extensive fibrinopurulent exudate. In a few areas of the meninges the cellular exudate consisted mainly of monocytes and lymphocytes. The cortical ganglion cells showed moderate chromatolysis. Early bronchopneumonia and acute splenitis completed the pathologic picture.

It might be mentioned that of the five patients recovering, three were 14 months of age or under. One of the interesting observations on treatment was the resistance of the cerebrospinal fluid to permanent sterilization. Patients receiving antiserum in initial amounts of 100 to 150 mg. of nitrogen showed a prompt fall in temperature curve, lowering of the cerebrospinal fluid cell count, and marked clinical improvement. This fall occasionally was permanent but frequently the improved symptoms lasted for a period varying from three or four days to ten or more days, then showed a gradual regression with slow recurrence of the infection. Necropsy by us of patients treated in the previous year with unconcentrated rabbit antiserum made in the School of Medicine here suggested that such recurrences arose from persistence of viable *H. influenzae* in residual small areas of fibrin deposits in the pia arachnoid spaces or in the cisterna magna which had become walled off by fibrin and thus rendered inaccessible to the action of antiserum. These recurrences were undoubtedly responsible for the long period of hospitalization, extending from twenty-five to seventy-five days in our five cases.

TABLE I

CLINICAL DATA OF TREATED PATIENTS

PATIENT AGE IN MONTHS, COLOR, SEX	RECOVERED					DIED			
	M. K. 14, W. F.	R. S. 44, W. M.	J. T. 11, W. M.	O. F. 24, W. F.	V. B. 12, B. M.	N. L. 18, W. M.	J. M. 12, W. M.	J. H. 13, W. M.	F. M. 5, W. M.
Weight on admission	28	30	22	32	19	26	28	36	15
Days illness on admission	5	2	6?	3	5	4	5	7	3.5
Days hospitalized	75	49	51	62	25	22	1	1.5	4
Days duration of fever	31	11	15	13	6	10	1	1	4
Influenzal otitis media	Bilat.	Neg.	Right	Neg.	Neg.	Left			Neg. ?
Influenzal mastoiditis	Left	Neg.	Right	Neg.	Neg.	Left		Left	?
								Post mortem	
Mastoid x-ray positive	Left	Neg.	Right	Neg.	Neg.	Left		Neg.	Bilat.
Mastoidectomy (simple)	Left		Right			Left		Positive	
								Post mortem	
Cerebrospinal fluid cell count on admission	4,080	5,760	600	5,000	1,100	1,760	2,600	3,000	22,000
Number of days before cerebrospinal fluid count below 100	7	7	9	13	8	4			
Number of days before cerebrospinal fluid cultures negative	1	6	2	1	1	4			
Times cerebrospinal fluid subsequently positive	2	2	0	1	0	2			
Urine albumin with treatment	+	0	++	Trace	0	++++			
R.B.C. in urine with treatment	0	0	++++			+			
Drug crystals in urine	0	0	++	0	0	++			

TABLE II

DRUG THERAPY

PATIENT	RECOVERED					DIED			
	M. K.	R. S.	J. T.	O. F.*	V. B.	N. L.†	J. M.	J. H.†	F. M.
Antiserum									
Total amount intrathecally in mg. N equivalents	75	25	112.5	50	50	50	25	25	25
Number of intrathecal doses	3	1	5	2	2	2	1	1	1
Total amount intravenously in mg. N equivalents		50		50	50	150	25	50	50
Number of intravenous doses		2		2	2	6	1	2	2
Total amount in mg. N equivalents	75	75	112.5	100	100	200	50	75	75
Capsule swelling with cerebrospinal fluid twenty-four hours after injection			Pos.	Pos.	Pos. Bl. serum	Pos.	Neg.	Neg.	Neg.
Sulfapyridine									
Total amount in grams	1,752	1,906	1,805	2,400	735		60	220	140
Total dosage per os	90	90	90	60	60		60	60	60
Number of days given	23	43	32	47	18		1	1.5	3.5
Average number of grams per day	5	3	4	3.4	2.7		4	13	2.6
2 per cent sodium salt intrathecally in c.c.	10	6							
Sodium salt intravenously in grains						115	30		30
Number of intravenous doses						3	1		2
Average concentration in cerebrospinal fluid in mg. %	7.4	1.4	2.4	3.5	10+	7.3			0.66
Highest concentration in cerebrospinal fluid in mg. %	12.5	3	7	5.2	25.3				
Lowest concentration in cerebrospinal fluid in mg. %	1	0.2	0.4	0.6	4.9				
Sodium Salt of Hydroxyethylapocupreine Hydrochloride									
Total amount of 1:1,000 solution in c.c.	75	100		60			2.5		10
Number of days given	16	7		12		1		1	
Average daily amount in c.c. intrathecally	5	7		5					

*Also received sulfanilamide.

†Also received sulfathiazole.

It was in the hope that B71 might be an additional factor in aiding sterilization of the spinal fluid that this chemical was used. In patient R. S. it was felt that this drug may have been measurably effective when it was used intrathecally once daily in amounts of 5 to 10 c.c. of 1:1,000 dilution. The spinal fluid cell count fell from 3,400 to 66 in seven days, but the culture remained positive. Although sulfapyridine was also given, the concentration of this drug in the spinal fluid did not attain more than 1.7 mg. per cent. Because this concentration is lower than the usually interpreted effective level of sulfapyridine, it was concluded that B71 also had some bacteriostatic effect. After ten days of combined B71 intrathecally and sulfapyridine per os, antiserum was begun, and in three days the temperature fell to normal and convalescence was uneventful thereafter.

Patient M. K. had a drop in spinal fluid cell count from 4,080 to 102 in four days with sulfapyridine and antiserum therapy. On the fifth day the cerebrospinal fluid count rose to 1,600; B71 was given intrathecally, and there was a prompt subsidence of cell count and symptomatology. Convalescence was long drawn out because of secondary infection in the incision of the left mastoidectomy which had been performed eight days after admission.

Patient O. F. was initially treated with sulfanilamide, because it was at first thought the organism responsible for her meningitis was meningococcus. Antiserum was administered, however, within twenty-four hours after admission. On the sixth hospital day when cells in the spinal fluid rose from 840 to 1,690 with report of a positive smear, the sulfonilamide dosage was increased and intraspinal administration of B71 was begun. A change to sulfapyridine was perhaps unjustifiably made when on the tenth hospital day the cell count had risen again from a low of 140 to 565. During the first ten days a total of 645 gr. of sulfanilamide with an average of 60 gr. daily was given by mouth. The highest concentration obtained in the cerebrospinal fluid was 16.6 mg. This case was remarkable for an up and down fever which persisted for twenty-one days thereafter during sulfapyridine therapy with a fluctuation in spinal fluid cells from around 80 to 200 from day to day. A 25 mg. equivalent of nitrogen dose of Squibb's serum given intrathecally at the end of this time resulted in severe febrile reaction and an increase in spinal fluid cells to 6,000 with a 4 plus globulin and positive culture. The next twenty-four hours the child again seemed much improved, cell count fell to 190, culture was negative, and convalescence from that time was uneventful.

J. T., surviving the vicissitudes of a right mastoidectomy and the appearance of sulfapyridine crystals, red blood cells and a 2 plus albumin in the urine six days after the institution of the drug, showed on his eighteenth day what appeared to be a developing spinal fluid block. Cell count of the spinal fluid had previously been reported down to 32. The

following day, however, the fontanel was noted to be quite tense, and the manometric reading of the spinal fluid was over 600 mm. of water pressure. The increased pressure persisted for several days, then subsided spontaneously with no apparent deleterious effects.

In the patient V. B. a spinal fluid concentration report of 19.4 mg. per cent sulfapyridine was thought to be in error due to possible contamination with novocain. Dosage was therefore not reduced. The following day an analysis performed after spinal tap in which no novocain was used revealed a concentration of 25 mg. per cent. The drug was drastically reduced. It is interesting that the only sign of drug intoxication was some restlessness of the patient. The urine and blood remained normal. This patient had previously received 70 gr. of sulfanilamide in less than two days with an average spinal fluid concentration of 3.5 mg. per cent. At the time of this report the five patients who recovered were in good health.

DISCUSSION

The use of anti-influenzal rabbit serum has markedly improved the prognosis in influenzal meningitis. A mortality of 44.5 per cent in this small series of nine patients is in the range of that accomplished by Alexander[2] in a larger series of patients. The meningeal irritation following the intrathecal use of serum, as indicated by the prompt increase in the cerebrospinal fluid cell count, raises the question as to whether the intraspinal injection is justifiable or whether the intravenous route may not be the route of choice. In three recent necropsies in this hospital following unsuccessful treatment with serum and sulfadiazine, together with one (J. H.) of this series, the presence of extensive fibrinous meningeal exudate makes us question whether intrathecal use of serum may not be conducive to the further formation of fibrinous exudate in the pia arachnoid. In patients who readily responded favorably to the serum, the spinal fluid became culturally negative in four to six days. The fever, however, sometimes persisted for six to fifteen days following the institution of serum therapy. A recurrence of symptoms after such a period of quiescence should immediately arouse suspicion of an unresolved focus of infection and especially in the mastoids or middle ears. The early diagnosis of an associated mastoiditis and the prompt eradication of this focus of infection is desirable. This complication was apparently the precipitating factor in three of the fatal cases as well as in two of the patients who recovered.

It is difficult to assess the part played by the sulfonamides in combating the infection and attaining the final sterilization of the meninges. The low diffusibility of sulfathiazole and the fact that crystals of this drug may appear in the kidney would indicate that sulfanilamide and sulfapyridine are to be preferred. The appreciable reduction of the cerebrospinal fluid cell count by the use of either of these two drugs in

the absence of serum indicates that they may be a valuable adjunct to serum treatment. Their use in conjunction with serum does not appear to have lessened materially the period of prolonged hospitalization or convalescence. Sulfapyridine given by mouth can be tolerated in large doses without obvious deleterious effect. It has likewise been difficult to determine definitely what bacteriostatic action if any was exerted by the intrathecal use of R71, but it is believed that this compound is worthy of further clinical study.

SUMMARY

1. A mortality of 44 per cent resulted in nine patients with influenzal meningitis who were treated with type-specific anti-influenzal rabbit serum* in conjunction with orally administered sulfapyridine in daily doses of 60 to 70 gr. An associated influenzal meningitis gave a grave prognosis unless mastoidectomy was performed.

2. Nine patients with type B influenzal meningitis with recovery in five are reported with such treatment. Of the four patients that succumbed, three were 13 months of age or under and in extremis at the time of admission. The fourth child, aged 18 months, lived twenty-two days and finally died of a sulfathiazole nephritis.

3. A level of 25.3 mg. per cent of sulfapyridine in the spinal fluid is not incompatible with either life or successful recovery.

4. The value of sodium salt of hydroxyethylapocupreine hydrochloride used intrathecally in conjunction with the above treatment in four patients is problematic but seems worthy of further clinical investigation.

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*E. R. Squibb & Sons.

NONSPECIFIC SEROLOGIC REACTIONS FOR SYPHILIS IN INFANTS AND CHILDREN

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FROM time to time on the services of the Infants' and Children's Hospitals, positive serologic reactions for syphilis have been noted in patients who by history and all other methods of examination have been adjudged free from the disease. This phenomenon is by no means limited to those in the pediatric group but has been recognized as occurring frequently in adults with yaws, leprosy, malaria, infectious mononucleosis, recurrent fever, typhus, and to a lesser degree, in tuberculosis, malignant neoplasms, vaccinia, acute bacterial infections, and jaundice. Rein and Frank,[1] in a review of the status of the serology of syphilis, stated that any severe metabolic disturbance might influence the reliability of such tests. Clifton and Heinz,[2] using the Kolmer-Wassermann, the Kahn, and the Eagle tests in a survey of prenatal syphilis in a hospital for sick children, found an incidence of 1.46 per cent of false positive tests, a majority of which were obtained from patients with respiratory infections. Mohr, Moore, and Eagle,[3] studying the occurrence of biologic false positive serologic reactions in tests for syphilis, noted, in a small group of patients, a rather high incidence of respiratory disease.

This survey represents a study of serologic data accumulated over a ten-year period from the records of patients in the Infants' and Children's Hospitals. The regular Hinton test[4] and the Davies-Hinton microflocculation test[5] were used exclusively; and inasmuch as both tests in United States Public Health Service evaluations attained comparable levels of sensitivity and specificity,[6] no distinction between the two methods has been made in the data which follows.

In the two hospitals a serologic test for syphilis is routinely made on all inpatients, whereas such serologic testing of outpatients is at the discretion of the outpatient physician. The specimens are sent to the Wassermann Laboratory of the Massachusetts Department of Public Health where the testing is done within twenty-four hours unless week ends or holidays intervene. The reports are then returned to the hospitals and transcribed on the records of the patients.

All patients with positive serologic tests, and determined to be syphilitic, are referred for treatment to the medical in- or outpatient services, depending upon the severity of the disease. Infants and children with positive blood tests, but with no other evidence of syphilis either in themselves or in their families, are retested at fairly regular intervals. In all instances these tests eventually became negative.

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COMMENT

It is desirable to point out that this presentation is in no way an evaluation of the Hinton and Davies-Hinton microflocculation tests, as the data does not truthfully adapt itself to this form of interpretation. It is hoped, however, that the attention of physicians dealing with infants and children may be drawn to the fact that serologic tests for syphilis may give nonspecific reactions in conditions other than syphilis. Positive or doubtful tests occurring during the neonatal period in infants born of adequately treated syphilitic mothers should cause no confusion. These are specific or true reactions occurring in normal children.[7]

TABLE I

TESTS RECORDED 1931-1941

TOTAL POSITIVE	TOTAL DOUBTFUL	TOTAL NEGATIVE	TRUE POSITIVE (SYPH.)	TRUE DOUBTFUL (SYPH.)	FALSE POSITIVE (TWO OR MORE TESTS)	FALSE DOUBTFUL (TWO OR MORE TESTS)	FALSE POSITIVE (SINGLE TEST)	FALSE DOUBTFUL (SINGLE TEST)
909	158	25,645	774	51	73	41	62	66

TABLE II

CLASSIFICATION OF SINGLE NONSPECIFIC POSITIVE OR DOUBTFUL REACTIONS, ACCORDING TO DISEASE

DISEASE OR CONDITION	POSITIVE	DOUBTFUL
Respiratory disease, acute and chronic	21	21
No disease	12	13
Acute infections	7	8
Patients postoperative, surgical and orthopedic	5	9
Nutritional disturbance, acute and chronic	2	2
Nephritis, pyelonephritis	2	2
Rheumatic fever, rheumatic heart disease	2	2
Miscellaneous	11	9
Total	62	66

Table I provides a summary of all the data collected and a breakdown of the false positive and false doubtful tests into single and multiple test groups. Table II classifies, according to disease or condition, those individuals in whom one positive or one doubtful serologic reaction was followed by repeatedly negative reactions. In this group the use of the terms "false positive" and "false doubtful" may be questioned, because a single reaction may have resulted from laboratory or clerical error as well as from the disease or condition of the patient. It must be noted, however, that one-third of this group has respiratory disease. This finding is consistent with the experience of others and will be borne out in the group of proved nonspecific reactions.

Table III presents in some detail thirty-seven patients from whom two or more nonspecific reactions, positive or doubtful, were obtained.

The data reveal no correlation between acute and chronic forms of disease and the duration of the nonspecific reaction. Two-thirds of the patients had some form of acute or chronic infection and one-quarter had respiratory infections. Two cases of ratbite fever had rather persistent positive and doubtful serologic reactions for syphilis.

TABLE III

FALSE POSITIVE AND FALSE DOUBTFUL TESTS (MULTIPLE)

CASE	POSITIVE	DOUBTFUL	LENGTH OF TIME TO BECOME NEGATIVE	DISEASE
1 (F. W.)	2	0	2 Weeks	Chronic upper respiratory infection
2 (I. T.)	2	1	9 Months	Chronic upper respiratory infection
3 (V. S.)	2	0	10 Days	Pneumonia, empyema
4 (C. B.)	1	2	2 Months	Hemolytic streptococcus pharyngitis
5 (I. M.)	2	2	4 Months	Hemolytic streptococcus pharyngitis
6 (M. B.)	6	1	9 Months	Bronchiectasis
7 (C. T.)	1	1	2 Weeks	Asthma
8 (H. R.)	1	1	1 Month	Scarlet fever
9 (A. D.)	1	2	2 Weeks	Hemolytic streptococcus mastoid
10 (G. E.)	2	0	6 Weeks	Nephritis
11 (M. C.)	0	2	1 Week	Nephritis
12 (P. C.)	0	2	4 Months	Nephritis
13 (F. S.)	1	1	2 Weeks	Pyelonephritis
14 (M. S.)	7	1	5 Months	Pyelonephritis
15 (D. M.)	5	1	2 Months	Ratbite fever
16 (A. F.)	7	1	3 Months	Ratbite fever
17 (T. D.)	3	0	1 Month	Chronic nutritional disturbance
18 (C. M.)	1	1	2 Weeks	Acute nutritional disturbance
19 (J. S.)	1	2	3 Weeks	Dysentery, Sonne
20 (A. D.)	2	0	10 Weeks	Scurvy
21 (J. P.)	3	0	7 Months	Idiopathic purpura
22 (G. H.)	0	3	2 Weeks	Acute Poliomyelitis
23 (F. G.)	0	2	1 Year	Old Poliomyelitis
24 (F. S.)	2	1	6 Weeks	Mercury ointment eruption
25 (A. M.)	1	1	6 Weeks	Convulsions
26 (A. K.)	2	1	2 Weeks	Celiac disease
27 (A. T.)	2	0	3 Weeks	Rheumatic fever and heart disease
28 (C. N.)	5	1	2 Months	Appendicitis, peritonitis
29 (S. S.)	0	2	10 Days	Neuroblastoma
30 (S. M.)	0	2	3 Weeks	Mental deficiency
31 (N. D.)	3	1	5 Months	Umbilical hernia repair
32 (C. S.)	1	1	3 Weeks	Inguinal hernia repair
33 (R. C.)	3	1	8 Months	Inguinal hernia repair
34 (E. G.)	1	1	1 Month	Cleft palate repair
35 (D. R.)	2	0	2 Weeks	Fracture, clavicle
36 (G. A.)	1	1	2 Weeks	Osteomyelitis, staphylococcus sepsis
37 (L. E.)	0	2	1 Week	No disease
Total	73	41		

SUMMARY

1. Approximately 26,700 Hinton and Davies-Hinton microflocculation tests have been tabulated from the records of the inpatient and outpatient services of the Infants' and Children's Hospitals.

2. Negative reactions were obtained from 25,645 presumably nonsyphilitic individuals. Two hundred and forty-two nonspecific reactions, positive and doubtful, are recorded. One hundred fourteen of

these tests obtained from thirty-seven patients represent proved false positive and proved false doubtful reactions. The remaining 128 tests are single positive or doubtful results which may be either nonspecific reactions or the consequence of laboratory or clerical error.

3. Respiratory infections in particular, and acute infections in general, make up a major portion of the nonspecific reactions noted in this study. False positive or false doubtful serologic reactions for syphilis may occur in a variety of other conditions.

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THE BISMUTH LINES OF LONG BONES IN RELATION TO LINEAR GROWTH

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ADMINISTRATION of bismuth in amounts such as are used in the treatment of patients with syphilis causes abnormal changes at the site of provisional ossification of growing long bones.[1, 2] These changes are of a nature that, when examined radiographically, the bone structure at the epiphyseal line appears more dense than the neighboring normal bone. With cessation of bismuth therapy bone formation at the metaphyseal line resumes a normal course, and with further bone growth the stria caused by bismuth appears to move along the shaft away from the epiphysis. With another course of bismuth therapy a new line of abnormal bone formation appears in the metaphysis. This in turn appears to move along the shaft by reason of subsequent normal bone growth at the metaphyseal line. A succession of courses of bismuth treatment gives rise to a series of cross striations radiographically more dense than the normal bone between them. As the striae become farther removed from the epiphyseal line, they gradually become less evident and finally disappear as the result of normal osteoclastic and osteoblastic activity. Eventually the bone appears entirely normal. The metaphyseal changes under consideration can occur only when bone is still in the process of growth. After the epiphysis has united with the shaft, new striae cannot appear.

The changes that take place at the metaphyseal line as a result of bismuth therapy appear to consist chiefly of the persistence of matrix substance beyond the time when normally it would be removed. Thus the line of provisional ossification becomes unusually broadened and produces a wide shadow on the radiograph.

Because these abnormalities occur at the area of growth of the long bones and because linear growth of the body is dependent on bone growth, it seemed of interest to determine if long-continued antisyphilitic therapy affects the stature of children. To this end data have been collected and are presented in Table I. The routine method of treatment of congenital syphilis adopted here includes hospitalization of patients for a nine-day period. Full doses of arsphenamine are given on the first, third, fifth, seventh, and ninth days. The dosage of bismuth, using bismuth subsalicylate in oil, has been 2 mg. of elemental bismuth for each kilogram of body weight. Three full doses of bismuth are given during the nine-day stay. Patients are admitted to the pediatric service for

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courses of antisyphilitic treatment at six- to ten-week intervals. Treatment is continued in this manner until the Wassermann test gives negative results and for a subsequent period. In exceptional instances the treatment may continue for as long as ten years.

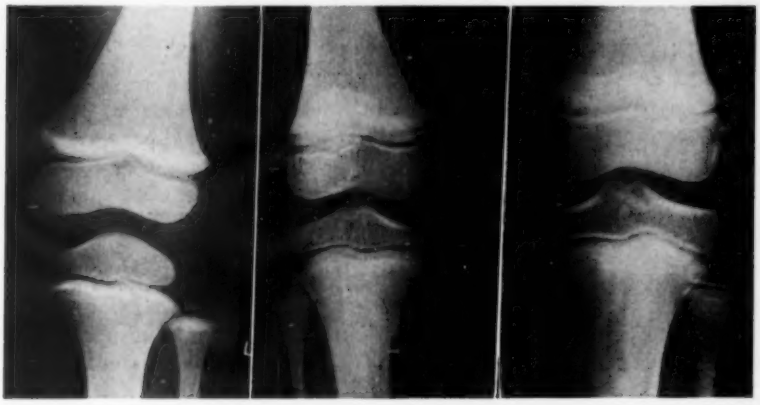

Fig. 1.—Bismuth lines as noted in the long bones of three patients under routine treatment. In each instance treatment had been carried out for at least seven months prior to the making of roentgenograms shown.

Fig. 2.—The knee area of a patient who had been under treatment for about seven years when the above roentgenogram was taken. No bismuth lines are in evidence, a fact attributable to failure of these lines to develop when the epiphysis in the region had fused.

Insults to the growing portion of bone, repeated frequently over a period of years, might conceivably affect the ultimate body length materially. However, we interpret our data as showing that the antisyphilitic treatment described has no adverse effect on ultimate bone or body

length. Of the children included in the study, the majority grew at average rates. Five exceeded the predicted height[3] by two or more inches and three had heights two or more inches less than those predicted. For the entire group the average difference between actual and predicted height is zero.

TABLE I

THE ACTUAL AND PREDICTED HEIGHT OF SYPHILITIC CHILDREN UNDER TREATMENT

PATIENT	AGE WHEN TREATMENT BEGAN (YR.)	AGE AT SUBSEQUENT OBSERVATIONS (YR.)	ACTUAL HEIGHT (INCHES)	PREDICTED HEIGHT (INCHES)
L. S.	9	10	51½	52
		11	55	54
C. M.	4¾	4¾	39½	41½
		6	44	44
R. VW.	2½	2½	34½	35¼
		4¾	36	41½
L. N.	1¼	3	39½	37
		4	42	40
R. H.	3¾	3¾	39¾	39½
		5	43	42
H. H.	12	13	57	57½
		14	59½	60¼
		15	62½	62
L. L.	10¾	11	53¾	54
		12	57	56
		13	59¾	58
		14	63	60
		15	64½	Not predictable
		16	65¾	
		16¾	66½	
M. A.	½	½	24½	26½
		2	32½	33½
W. H.	6¾	7½	46¾	47
		9½	52½	52
J. L.	7	7	48	46
		7¾	50	47¾

SUMMARY AND CONCLUSIONS

Lines of increased radiographic density occur in the metaphyses of growing bones as a result of bismuth medication, but not in bones whose growth has ceased as indicated by a fused epiphysis. Though the metaphyseal changes represent abnormalities of bone growth, they apparently do not retard growth in length. Even prolonged bismuth administration does not interfere with the rate of linear growth. Treated syphilitic children attain their predicted height based on age.

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SALICYLATE INTOXICATION IN INFANTS AND CHILDREN

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IN THE past eight years there have been seen at St. Louis Children's Hospital five patients in whom the diagnosis of salicylate poisoning was made. In four of the five cases the intoxication resulted from intensive therapeutic use of the salicylates, which, together with reports in the literature of similar poisonings,[1, 2] indicates the importance of the often repeated warning that the salicyl compounds are not always the harmless household remedy that they are supposed to be. The striking similarity of the clinical pictures in these five cases and the acuteness of the medical emergency which they presented aroused our interest in this subject. The paucity of recent clinical studies in the American pediatric literature prompted us to report these cases and to discuss the treatment which would seem to be indicated in view of our present knowledge concerning this intoxication.

The pertinent facts concerning the histories and findings of the cases presented are shown in Table I.

Salicylate Administration.—In four of the five cases, the symptoms of intoxication developed during the therapeutic administration of salicylates. The quantities of salicylate taken by these four cases, as shown in Table I, were estimated to be between 0.07 and 0.17 Gm. per kilogram per twenty-four hours, and the symptoms usually occurred within twenty-four hours after the administration was begun. These figures for the amounts taken were estimated from the histories and therefore are not strictly reliable due to possible inaccuracies in the statements of the informants. The figures given in Table I refer to the minimum amount estimated. The usually recommended dose of aspirin during infancy is 1 gr. per year of age,[3] which would be approximately 0.04 Gm. per kilogram per twenty-four hours if the dose were repeated every four hours. The quantities apparently taken by these patients showing intoxication ranged from only two to four times the recommended dosage. It would appear from this, as well as from the fact that comparatively large dosages are commonly given with no signs of intoxication, that factors in addition to the amount of salicylate ingested influence the occurrence of these symptoms. This will be discussed later. It is noteworthy, however, that in only one of the cases was less than two times the recommended dosage given.

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TABLE I

DATA ON HISTORIES AND CLINICAL FINDINGS ON ADMISSION OF FIVE CASES OF SALICYLATE INTOXICATION

CASE	AGE	WEIGHT (KG.)	CONDITION FOR WHICH SALICYL COMPOUND WAS GIVEN	INTERVAL BETWEEN BEGINNING OF DRUG ADMINISTRATION AND ONSET OF SYMPTOMS (DAYS)	AMOUNT OF DRUG TAKEN				TEMPERATURE ° C.			W.B.C.	SYMPTOMS AND FINDINGS										
					ACETYLSALICYLIC ACID		SODIUM SALICYLATE		ON ADMISSION	MAXIMUM	DURATION		HYPERPNEA	VOMITING	IRRITABILITY	STUPOR	DEHYDRATION	ANOREXIA	THIRST	CONVULSIONS	CYANOSIS	ACETONE ODOR	ABDOMINAL PAIN
					TOTAL GM.	GM./KG. PER DAY	TOTAL GM.	GM./KG. PER DAY															
R. C. J-2602	20 mo.	11	Accidental	2	?	?	?	?	37.0	38.1	3	42,500	×	×	×	×	×			×	×		
J. F. P-2335	8 mo.	8	Upper respiratory infection (bronchitis)	1	1.5	0.06 for three days	1.8	0.075 for three days	39.0	39.6	2.5	14,000	×	×	×	×	×					×	
J. L. Q-2641	2 yr., 9 mo.	13.5	Upper respiratory infection	1	4	0.07 for 4.4 days	6.2	0.10 for 4.4 days	37.7	38.9	5	13,200	×	×	×	×	×	×					
J. B. R-1049	5 yr., 10 mo.	18.0	Post tonsillectomy	6	14.6	0.09 for five days 0.22 for one day	--	--	37.6	38.0	1.8	10,200	×		×	×	×	×				×	×
P. B. R-2296	1 yr., 1 mo.	8.5	Upper respiratory infection	1	0.6	0.07 for one day	--	--	39.2	40.6	5	14,000	×	×	×	×	×	×		×	×	×	

TABLE II

RESPONSE TO TREATMENT OF ACIDOSIS OF SALICYLATE INTOXICATION IN FOUR PATIENTS WHO HAD RECEIVED SALICYL COMPOUNDS FOR THERAPEUTIC PURPOSES

CASE	DATE	TIME	TREATMENT: SODIUM R-LACTATE I. V. (C.C.)	TREATMENT: SODIUM R-LACTATE SUBCUT. (C.C.)	TREATMENT: RINGER'S C.C. SUBCUT.	TREATMENT: DEXTROSE 10% C.C., I. V.	BLOOD SERUM: CO_2 (VOL. %)	BLOOD SERUM: pH	BLOOD SERUM: N.P.N. (MG. %)	BLOOD SERUM: SUGAR (MG. %)	URINE: REACTION	URINE: KETONE ACIDS	HYPERVENTILATION	REMARKS
J. F.	11-11-39	2:30 P.M.					15.4			69	Acid	+	+	
		3:00 P.M.	180 M.*/3	450 M./6	360								+	
		11:15 P.M.					35.0						+	
	11-12-39	11:00 A.M.					36.1						+	
		1:00 P.M.	200 M./6	200 M./6									±	
	11-13-39	11:00 A.M.					55.0						-	
	11-16-39												–	Discharged recovered
J. L.	12-16-40	10:30 A.M.					25.0	7.34	35.2	90.0	Acid	+	+	
		11:00 A.M.	420 M./6	420 M./6	560								+	Epinephrine M 3
		2:40 P.M.	6.7 M		300								+	
	12-17-40	8:30 A.M.					28.0					+	+	
		12:30 P.M.	10 c.c. M., orally										+	
		3:30 P.M.	420 M./6									+	+	
		4:00 P.M.	35 c.c. M., orally											
	12-18-40	to 8:00 A.M.											+	Scarlatiniform eruption; ? drug eruption
		9:15 A.M.					67.0	7.52			Alk.		–	
		11:30 A.M.				250							–	Insulin units, 2.5
		11:00 P.M.											–	28 c.c. 2% sodium sulfapyridine q. 4 h. by rectum for U.R.T. infection

	12-19-40	11:00 A.M.				250						–	–	Insulin units 2.5
	12-23-40												–	Discharged recovered
J. B.	6-10-41	8:30 P.M.					28.9				Acid	+	+	
		9:30 P.M.	400 M./6	800 M./6									+	
	6-11-41		10 c.c. M., orally q. 4 h.										+	
	6-12-41												–	Discharged recovered
P. B.	10-14-41	1:00 P.M.					26.6		45.0	107.0	Acid	+	+	
		1:30 P.M.	250 M./6	250 M./6	250								+	
		4:30 P.M.					31.6						+	
		6:00 P.M.	120 M./6			100							+	60 c.c. O. J. + 15 Gm. dextrose, orally, q. 2 h.
		10:30 P.M.					36.4						+	17 c.c. 2% sodium sulfathiazole, I.V., sulfathiazole, 0.325 Gm. q. 4 h. by mouth
	10-15-41	2:15 A.M.					40.1						+	
		4:30 A.M.	260 M./6										+	
		9:00 A.M.					61.0				Acid (6.2)	+	±	
		10:00 P.M.		10 M.	250	250	65.0				Acid (6.2)	+	–	
	10-16-41	12:35 P.M.							21.0	93.0	Acid (6.2)	+	–	
	10-17-41	1:00 A.M.									Alk. (7.5)	–	–	
	10-23-41												–	Discharged recovered

*M. = Molar.

Clinical Picture.—The outstanding clinical manifestation in these cases was the intense hyperventilation which, in all of them, suggested the severest type of acidosis. The presence of this hyperventilation in an infant or child who is not severely dehydrated, and in whose history is found none of the usual causes for acidosis, suggests salicylate intoxication. The diagnosis was tentatively made in two of the four cases receiving the drug therapeutically before any laboratory data was obtained, and in one of the four cases on the appearance of the child alone. *Dehydration* of some degree was noted in every case, but it was usually mild. It was frequently remarked by the first observer of the case that the dehydration was not in proportion to the apparent degree of acidosis, and in one case sodium r-lactate was given in a more concentrated solution than usually employed because of the mildness of the dehydration. *Vomiting* had occurred in all but one case and was usually severe. *Stupor,* associated with periods of *irritability,* was present in all five cases. *Generalized convulsions* occurred in two cases. *Cyanosis* was observed in two of the cases. An *acetone* odor of the expired air was detected in three of the cases. One patient complained of *abdominal pain.* In three of the five cases the temperature was not significantly elevated. *Fever* was present on admission in two instances, but the infections for which the drugs were given were still present. *Tinnitus* was reported in only one case. *Thirst* and *polyuria* were not mentioned in the histories obtained, possibly because of the age of the patients.

Laboratory Findings on Admission.—The important laboratory findings on admission are included in Table II. The values for the carbon dioxide content of the blood sera in the four cases in which the salicyl compound was given therapeutically and in which the intoxication was well developed on admission varied from 15.4 to 28.9 volumes per cent. In one case, J. L., the pH of the serum on admission was 7.34 at a time when the carbon dioxide content was 25 volumes per cent, the significance of which will be mentioned later. In three of the cases in which serum nonprotein nitrogen determinations were done on admission, the values were 28, 35.2, and 45 mg. per cent. Blood sugar determinations on four of the five cases were within normal limits on admission. In the case of R. C. the distillate of the protein-free filtrate of the blood serum obtained by heating before the addition of potassium permanganate in the determination of lactic acid gave a heavy cloud when caught in Scott-Wilson's reagent, which served as a qualitative test of marked increase in blood acetone.

In each of the cases, the urine was acid on admission and gave a strongly positive test on addition of ferric chloride, which persisted after acidification and boiling. The Rothera test for acetone was strongly positive, and the distillate of the urine specimen from R. C. gave a heavy cloud when tested with Scott-Wilson's reagent. In one case the urinary sediment showed no formed elements on microscopic examina-

tion, and in the other four only white blood cells were present in small numbers.

In one case, P. B., in which a lumbar puncture was done, the spinal fluid was crystal clear, contained no increase in cells, gave a strongly positive test with ferric chloride, and the carbon dioxide content was 19.5 volumes per cent (blood was 26.6 volumes per cent).

DISCUSSION AND TREATMENT

Treatment of salicylate intoxication must be generally directed toward correction of the important changes which have taken place. A description of these changes and of the mechanism involved in the production of them has been the subject of numerous investigations and must primarily consider the following factors:

1. The explanation for the intense hyperpnea, which is the outstanding clinical manifestation.
2. The failure to relieve the acidosis, when present, by the administration of the usual quantity of alkali.
3. The occurrence of symptoms of intoxication in some patients who receive quantities of salicyl compounds which are easily tolerated by other patients.

The data obtained in our cases which relate to these factors can be presented in the following considerations.

In the only case (J. L.) in which a pH measurement of the serum was made, it was found to be 7.34 at a time when the carbon dioxide content of the serum was 25 volumes per cent. This corresponds to the type of change in the acid-base balance observed in this laboratory[4] after the administration of large doses of sulfanilamide,* and suggests the occurrence of a carbon dioxide deficit type of alkalosis produced by hyperventilation. The occurrence of primary hyperventilation during salicylate administration has been observed by numerous investigators and has been attributed to direct central stimulation of the respiratory center by salicyl compounds[2] and to the changes in temperature, the sensation of heat, and the increase in gaseous exchange induced by the salicylates.[1] Whatever the direct cause of the stimulus to respiration, it seems well founded that the intense hyperpnea early in the course of salicylate intoxication is due almost wholly to central stimulation of respiration since it may occur before any fall in the carbon dioxide content of the serum is observed.[2] Later in the course of the intoxication, when acidosis does develop, the effect of this specific central stimulation is added to the stimulation of respiration by the acidosis (see below) and the characteristic intense hyperpnea is produced.

*It has been shown by Beckman and his co-workers[5] and confirmed in this laboratory that primary hyperventilation cannot account for all of the changes in acid-base balance following sulfonamide administration, since the urine becomes alkaline before an increase in air exchange is observed by direct measurement. Neither of the conflicting views which has been offered to explain the type of alteration and the cause of this change in the acid-base balance after sulfanilamide administration is adequate, and it is still our impression from our data that primary hyperventilation from a direct central stimulation to respiration by sulfanilamide plays an important role.

The use of sodium r-lactate in the treatment of acidosis in salicylate intoxication has been reported by Williams and Panting[6] to bring about rapid improvement in the clinical condition and by Shirreff and Pearlman[7] to produce no startling results. The results of the treatment of the acidosis with sodium r-lactate in our cases is shown in Table II. The subject has been discussed in full by Hartmann and his co-workers[8] in the case of R. C. which is included in this series and whose course during treatment is shown in Chart 1. As was pointed out by Hartmann and his associates, the expected rise in the carbon dioxide content of the serum did not occur with sodium r-lactate. However, as is also shown in Chart

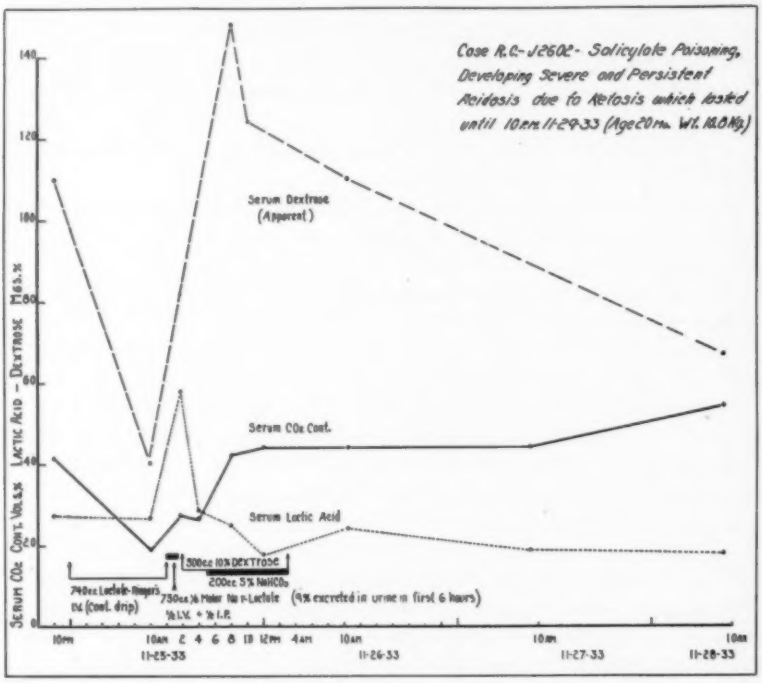

Chart 1. Response to treatment of acidosis of salicylate intoxication in a patient who had received a salcyl compound accidentally.

1 by the curve of serum lactic acid following the administration of sodium r-lactate, the lactate was normally metabolized. Because of this, and particularly because the expected rise did not follow the intravenous administration of sodium bicarbonate either, it was concluded that the failure to correct the acidosis was due to the fact that the amount of alkali given was quantitatively insufficient to offset completely the base-finding effect of the ketone acids. Additional data obtained from the blood and urine of case R. C. and the urines of cases P. B. and J. L. confirm the belief that the accumulation of ketone acids was unusually per-

sistent and intense. Ketone acids were demonstrated in large amounts in the blood of the patient R. C., by the method previously mentioned, until Nov. 28, 1933, which, as can be seen from Chart 1, was three and one-half days after treatment was begun. The ketone acids persisted in the urine of this patient until Nov. 30, 1933, which was five days after the beginning of treatment. In the cases of P. B. and J. L., ketone acids persisted for four and three days, respectively. Our data fail to show evidence of significant nitrogen retention or lactic acid accumulation, so that the acidosis in these cases could not be explained on the basis of renal or cardiac failure.

Acidosis, of the type described, due to intense ketosis was present in each of the five cases here reported, and the improvement in the clinical condition of the patients corresponded so closely with the correction of the acidosis that we feel that this is the most important phase of treatment. Although the earliest change in the acid-base balance is of the carbon dioxide deficit type of alkalosis, this change is apparently quickly reversed by the development of ketosis, and a true metabolic acidosis develops.

In the case of R. C. the pH of the urine, as determined by indicators, rose from about 5 during the acidosis before treatment was started to between 6 and 7 before the carbon dioxide content rose to normal.* This would indicate that the primary stimulation of respiration by the salicylates had persisted, since one would have expected the urinary pH to remain of maximum acidity until the carbon dioxide content of the serum had become normal unless primary hyperventilation was continuing.

The ketosis was more intense and particularly more persistent than could be expected merely from starvation due to vomiting for such short periods under normal circumstances. It suggested the possibility that there may have been some specific inadequacy of carbohydrate metabolism. This suggestion was strengthened by the fact that *hypoglycemia*† was actually observed to have occurred in the case shown in Chart 1. In view of the experimental work of Dodd and her co-workers[2] in which they showed an increase in the metabolic rate following salicylate administration, this would suggest that salicylates may specifically cause a rapid depletion in the glycogen reserve of the body. This glycogen depletion would be augmented by low carbohydrate intake due to poor appetite during the illness for which the salicylate is being given and to vomiting, and would allow ketosis to occur with inordinate rapidity. This conception does not account for differences in the susceptibility of

*A case of salicylate intoxication recently studied by Doval[8] at St. Louis City Hospital showed this strikingly. On admission, the pH of the urine was 4.5 and the blood carbon dioxide content was 36 volumes per cent. Three hours after the administration of sodium lactate the patient still showed marked hyperpnea, but the urine pH was 7 and remained there even though seven and one-half hours later the carbon dioxide content of the serum had risen only to 44 volumes per cent.

†The value shown in Chart 1 as 40 mg. per cent for the blood sugar is in terms of apparent blood sugar; a simultaneous determination of true blood sugar was found to be 25 mg. per cent.

patients to the original primary hyperventilation. It may explain, however, the sporadic occurrence of salicylate intoxication on the basis that susceptibility may depend on the adequacy of glycogen reserve when salicyl compounds are given.

Dodd and her co-workers[2] have emphasized the importance of treating dehydration and hyperpyrexia in cases of salicylate intoxication. Since neither of these findings was prominent in our cases, we should feel that the treatment of them becomes of secondary importance. On the basis of our observations, the most important phases in the prevention and treatment of salicylate intoxication would appear to be:

1. Avoidance of the therapeutic administration of quantities of salicyl compounds above the recommended dosage and the provision of adequate carbohydrate intake during the period of administration would appear to be most important in prevention.

2. Treatment of the acidosis with adequate amounts of alkali, repeated as often as necessary, would seem from our data to be the most important phase of treatment. Alkali can be safely and preferably given in the form of sodium r-lactate,[9] since it has been shown to be metabolized in the presence of salicylate intoxication. If it is not possible by frequent examinations of the carbon dioxide content of the serum to determine the amount required, it would have to be judged on clinical response, but one should be prepared to give many times the usual amount. If the dehydration is very mild, one-third molar solutions of sodium r-lactate may be preferable to the usual one-sixth molar.

3. The administration of large quantities of carbohydrate seems indicated. Because of the frequent and severe vomiting, this is best given in the form of intravenous dextrose. The sodium lactate will also serve to supply available carbohydrate.

4. Steps 2 and 3 would also relieve dehydration and would hasten elimination of the drug.

5. Measures directed toward reduction of hyperpyrexia, if present, would be desirable, as suggested by Dodd and her co-workers.

6. Treatment of the infection for which the salicylates were given should not be neglected.

SUMMARY

1. Five cases of salicylate intoxication are presented.

2. In four of the five cases the intoxication occurred during therapeutic administration of the salicyl compound.

3. Unusually large quantities of alkali may be required to correct the acidosis of salicylate intoxication because of the intense and persistent ketosis.

4. The importance of glycogen depletion specifically associated with the increased metabolic activity due to salicylates in the development of ketosis and acidosis is suggested, and the effect of this on prevention and treatment of the intoxication is discussed.

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NITROBENZENE POISONING

Report of a Case Due to Exterminator Spray

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A. R., a female infant 12 months of age, was referred to one of us (R. P. F.) by Dr. Earl Underwood on Dec. 22, 1941, because of fever and apparent cyanosis. Shock from a recent fall on the head was a suspected cause for the dusky color which was most marked on the mucous membranes. Although the temperature was 103.4° F. (39° C.), the child did not appear to be as ill as the fever would suggest. She had been quite well, and her behavior was normal until twenty-four hours prior to admission when she began to refuse food and fluids.

The family history and the child's past history were irrelevant. The developmental history was that of a normal child. There was no history of exposure to a respiratory infection nor had the infant exhibited any cough, coryza, or constitutional symptoms other than the fever and change of color. The family had recently moved into a house infested with bedbugs. An exterminator company was engaged to rid the house of these unwelcome tenants and had sprayed the premises, including the baby's crib and mattress, at 11:30 A.M., Saturday, Dec. 20, 1941. No cyanosis was noted until the following morning and no fever until the second day.

A diagnosis of methemoglobinemia was made and the patient was referred to Children's Hospital. Blood was drawn for examination and the patient placed in an oxygen crib. Spectrophotometric study of the blood by Dr. E. I. Dobos demonstrated mononitrobenzene with methemoglobinemia. The exterminator spray contained four ingredients, including oil of mirbane or mononitrobenzene (12.5 per cent). The other ingredients were kerosene, turpentine, and oil of lilacine.

Laboratory Data.—The admission blood count was recorded as hemoglobin, 110 per cent; erythrocytes, 4,300,000; and leucocytes, 12,500 with 52 per cent neutrophiles. The total leucocyte count gradually fell to 8,600 and the neutrophiles to 28 per cent. On two occasions, December 26 and 27, 18 and 12 normoblasts were noted in counts of 100 leucocytes.

A roentgenogram of the chest on the second day showed that "the parenchyma of the lungs are quite clear and the heart and mediastinum are negative."

Treatment consisted of oxygen, one intravenous injection of 5 per cent dextrose solution of 200 c.c., and two blood transfusions of 150 c.c. and 120 c.c. on the third and fifth hospital days. A low-protein, high-carbohydrate diet was given, and the patient ate fairly well. Several warm soda colonic irrigations were given. On the fifth day, following the second transfusion, the irrigation fluid returns were pinkish in color. On the sixth day, an erythematous rash was noted on the head, back, and chest. The rash became maculopapular, spread over the entire body, and faded after forty-eight hours. During this time, the patient was quite irritable and refused most of her food. Oxygen was discontinued on December 28, the seventh hospital day.

The temperature fluctuated between normal and 104.2° F. (40° C.), the highest peak being noted on the third day, after which the temperature gradually fell to normal on the sixth day. During the first five days, the cyanotic color was intensified when the patient was taken out of oxygen. The child's color gradually returned to normal about the tenth day. On the twelfth day, a rise of temperature to 102°

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for twenty-four hours was followed by evidence of an upper respiratory infection and mild diarrhea. The patient was discharged in good condition on Jan. 9, 1942, seventeen days after admission.

Since spectroscopic examination of the blood from this patient revealed methemoglobin and nitrobenzene bands, we are certain that the poisoning resulted from absorption and inhalation of the oil of mirbane found in the bedbug exterminator spray. Nitrobenzene, essence of oil of mirbane, and imitation oil of bitter almonds, prepared by mixing pure benzene with sulfonitric acid, are synonymous. This product is used extensively in the manufacture of aniline and of explosives, as a substitute for benzaldehyde (oil of bitter almonds) in perfumery and flavoring extracts, as an ingredient of shoe dyes, floor polishes, etc. In reviewing the literature, its toxic effects are encountered most frequently as the result of absorption from shoe dyes. However, many severe and fatal cases of poisoning have resulted from its being taken internally when used as a substitute for flavoring agents, as in alcoholic liquors, in confections, or pastry. It has been taken as an abortifacient and as a means of committing suicide. Toxic absorption has occurred when nitrobenzene is spilled on clothes. Poisoning has resulted from inhalation of nitrobenzene vapors in industry. In 1886, Rayner[1] recorded seventeen instances of sudden onset of cyanosis in a London hospital for infants which was traced to diapers and pads freshly stamped with nitrobenzene. Poisoning has resulted from its application to the skin in treatment of scabies or as a delousing agent. Stevens[2] reports poisoning in 3-week-old twins from inhalation of vapors of "Cresco," containing nitrobenzene, used as a bedbug spray on the edges of the mattress on which the children slept. Other accidents have been reported from its application to a carious tooth instead of oil of cloves; also from soap (almond glycerine soap) scented with nitrobenzene. Muehlberger,[3] analyzing forty-eight cases up to 1925 which were reported in American and European literature, found that nitrobenzene was the toxic agent in twenty-five American cases and aniline predominated as the toxic agent in Europe. Riviere[4] reported eleven cases of cyanosis in children from 1½ to 11 years of age following the use of shoe dye, and Muehlberger reported two cases in children 3½ and 9 years of age, respectively. Levin[5] reports two cases resulting from absorption from shoe dye in infants 8 months old and 2 years old, respectively. Isbell,[6] between 1848 and 1876, reported forty-two cases with thirteen terminating fatally, while Stifel[6] reported seventeen cases resulting from shoe dye in an army camp. Stone[6] records a fatal case from shoe dye poisoning. There are other single reports, but those we have cited here include most of the cases reported in the English and American medical literature. The case reported by Stevens was of interest to us because of the similarity of circumstances. In both instances, the mattress had been sprayed. Stevens attributed poisoning to

inhalation, whereas we suspect absorption through the skin as the mode of entrance.

Properties.—Nitrobenzene, $C_6H_5NO_2$(NO_2), is an oily liquid of pale yellow color having the specific gravity of 1.205. It is volatile in steam, soluble in about five hundred parts water, freely soluble in alcohol, benzene, ether, and oils. The liquid burns readily with a luminous flame and has a sweet taste and an odor strongly resembling oil of bitter almonds.

Physiologic Action.—This is quite complex and is still a matter of conjecture. Central nervous system stimulation is followed by depression. There is no doubt that methemoglobinemia occurs and can be confirmed by spectroscopic examination of the blood. The blood becomes chocolate colored; many corpuscles are destroyed, while others are deformed. The blood becomes incapable of carrying oxygen and may contain only 1 per cent oxygen instead of the normal 17 per cent. The carbon dioxide combining power is decreased. There are usually a leucocytosis with a shift to the left, decreased hemoglobin, secondary anemia, anisocytosis and poikilocytosis.

Symptoms.—When taken internally, there develops a burning sensation, followed by numbness and tingling. Other symptoms may not occur for from fifteen minutes to two to three hours. The patient may walk about, eat, and appear normal until the sudden onset of symptoms. The face becomes grayish or bluish white, lips and neck become purple, the pulse becomes weak and rapid, the vision disturbed, and the gait unsteady, and the breath has the odor of bitter almonds. Vomiting, dizziness, and headache follow. Coma may appear quite suddenly and is invariably followed by a fatal termination. Muscular twitchings and incontinence may occur. Trismus may make difficult the passing of a stomach tube. The temperature may be subnormal and respirations are frequently of the Cheyne-Stokes type. Pupils may be dilated or contracted and do not react to light. There may be nystagmus. Urine is dark, smells of nitrobenzene, and contains a reducing substance. Blood is chocolate colored, thick, and viscid. The patient usually dies in coma or respiratory failure, often from aspiration of vomitus.

Patients surviving through several hours of acute symptoms may make a rapid recovery. Nausea and vomiting may persist, and there is a frequent rise in temperature, sometimes associated with necrosis, the latent result of poisoning, especially in the extremities, due to vascular damage.[7] Jaundice may appear in three or four days.

If absorbed through the skin or lungs, symptoms may occur very quickly. The patient may become dizzy, faint, and collapse in a few minutes, with death occurring in an hour. In less acute cases, there are drowsiness, faintness, headache, and unsteadiness of gait. The patient acts intoxicated and stuporous; the face is flushed and cyanotic. There

are cardiac irregularity, loss of voluntary power, and extreme cyanosis. The development of these symptoms is insidious. Coma may appear very suddenly with symptoms resembling those of vascular collapse, death being preceded by Cheyne-Stokes respiration and occasionally by convulsions.

In industry, men working with nitrobenzene frequently suffer from a form of chronic poisoning in which languor, somnolence, breathlessness, cyanosis, and sometimes failure of sight, are common symptoms. The urine is dark maroon in color and, on warming, gives an odor of nitrobenzene. Adams[7] reported a case of chronic poisoning extending over years in a woman who used nitrobenzene as a cleansing agent for hands and clothes. This was accompanied by fatigue, multiple neuritis, extreme indigestion, emaciation, and anemia.

Fatal Dose.—Fifteen drops of nitrobenzene have proved fatal. In one case, 23 minims taken in seven doses during forty-eight hours caused extremely alarming symptoms. With prompt treatment, one patient recovered after ingesting 3½ ounces. It is the consensus of opinion that there is 20 per cent mortality in all cases of nitrobenzene poisoning. However, since infants cannot offer their complaints of pharyngeal irritation, headache, or vertigo, exposure to poison is of longer duration and the prognosis worse. In these cases, poison by absorption is the most common route, the symptoms are more insidious, and Rayner[1] records a 37 per cent mortality.

Death has resulted within an hour from inhalation or absorption through the skin and within three hours after the poison has been taken by mouth. In most instances, it has occurred within twenty-four hours but occasionally has been delayed forty-eight hours or longer. In one instance, death did not occur until the seventeenth day.

Treatment.—When nitrobenzene is taken by mouth, gastric lavage with plain water should be continued until the smell of nitrobenzene cannot be detected. A saline purge may delay further absorption. Alcohol favors absorption. Oils, milk, and alcohol should not be given. If the poison is on the skin, a cleansing bath should be given. Respiratory stimulants should be prescribed as needed, preferably coramine. Blood transfusions are indicated and good results have been obtained with exsanguinating transfusions. Oxygen should be used in the early stages of cyanosis.

Therapeutically, the intravenous injection of glucose seems to be directly beneficial in the treatment of methemoglobinemia. This has been confirmed experimentally on animals. Apparently, glucose has an inhibitory effect on methemoglobin formation.[8]

The use of 1 per cent methylene blue solution intravenously has proved to be definitely beneficial. Fifty to 150 c.c. of 1 per cent solution was injected with almost instantaneous disappearance of cyanosis and other subjective symptoms. Investigation with rabbits and other laboratory animals throws no light on the mechanism of methylene blue action

in the blood. Recently, however, since the advent of sulfonamide drugs with resultant methemoglobinemia, it is supposed that methylene blue oxidizes methemoglobin to oxyhemoglobin. The dosage is 1 to 2 mg. of 1 per cent solution of methylene blue per kilogram of body weight. Oral dosage is 1 to 2 Gm. of methylene blue every four hours, depending on the patient's size.[10]

Differential Diagnosis.—Poisoning from large doses of phenacetin, acetanilid, and other coal tar derivatives and prussic acid may give a clinical picture similar to nitrobenzene poisoning. Potassium chlorate in toxic doses may produce a methemoglobinemia.

Spectroscopic examination of the blood for nitrobenzene gives a conclusive diagnosis. Examination of the urine, feces, and gastric contents for nitrobenzene is also indicated.

Medicolegal Aspect.—A federal statute established in 1906, governing the use of insecticides and fungicides, requires the registration of the formula of any substance used and the labeling of the percentage content of all active ingredients. However, a Colorado State insecticide and fungicide law was not put into effect until June, 1941, and no appropriations were made to carry out this enactment.

There is no United States Pharmacopoeia or National Formulary preparation containing nitrobenzene. However, *Merck's Manual* mentions the use of nitrobenzene in the treatment of scabies. The Federal Food, Drug, and Cosmetic Act prohibits its use as a preservative, medicinally for internal consumption, and in the manufacture of soap, shoe dyes, perfumes, and other cosmetics.

SUMMARY

1. A case of mononitrobenzene poisoning due to exterminator spray is reported.

2. Nitrobenzene is used in many commercial preparations, and numerous instances of poisoning have been recorded. The commonest of them is "shoe dye poisoning."

3. The symptomatology and treatment of nitrobenzene poisoning is briefly discussed.

4. In every case of cyanosis of obscure etiology, poisoning with nitrobenzene should be considered.

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HEREDITARY ECTODERMAL DYSPLASIA OF THE ANHYDROTIC TYPE

A Report of Two Cases

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MacKEE and Andrews[1] have described the clinical characteristics of hereditary ectodermal dysplasia of the anhydrotic type. These authors have listed as the outstanding features which these patients present the absence of the sweat and pilosebaceous glands, dental dysplasia, depressed nasal bridge, atrophic rhinitis, prominent supra-orbital ridges, and thick, protrusive lips. The skin has been described as thin, glassy, smooth, and dry, with papular lesions; also these individuals show a marked intolerance to heat.

The present report concerns two patients having this complete syndrome. A third patient with a partial syndrome is presented because of the rarity with which the disease occurs in sisters. I. J., having been adopted in infancy by another family, has a different last initial. These patients are all derived from the same family in which eight individuals were afflicted. Chart 1 shows the relationship between the three patients and the five other members of the family who were similarly affected. This report is restricted to the persons examined in this clinic.

CASE REPORTS

S. F. first entered the pediatric clinic, University of Iowa Hospitals, on Dec. 20, 1932, because of high fever, loss of appetite, and respiratory difficulty accompanied by cyanosis. It was said that his condition at birth had been poor and that blood transfusions became necessary immediately. The patient had presented a feeding problem since birth. The administration of cod-liver oil and orange juice had dated from the time the boy was 4 months of age. His development had been normal with the exception of delayed dentition; the first tooth erupted when he was 10 months of age. Pneumonia, which had developed on two different occasions, and chickenpox were the only other diseases he had had.

It was recalled that the patient had had snuffles from the time of birth, frequently his respirations had been labored, and cyanosis had occurred as well as sneezing and the expulsion of large crusts of dried secretions from the nose. While his temperature had ranged as high as 107° F., perspiration had been conspicuously absent. Heat intolerance and thirst had been marked. On Dec. 6, 1932, he was ill with recurrence of the high fever. This illness lasted for two days, and there was a similar episode some ten days later.

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Physical examination showed the nutritional state to be good. The skin was peculiarly white and the scalp hair was scanty. The frontal bosses were prominent and the nasal bridge depressed. While the patient cried a great deal, tears were absent. The nasal mucous membrane was dry and crusted. The lips were thick and protrusive and the buccal mucous membrane was dry. Eight teeth were present, four primary molars, and four primary incisors; only two teeth, primary molars, were present in the lower arch. All teeth showed coronal constriction toward the morsal surfaces. Tonsillar hypertrophy was of a moderate degree.

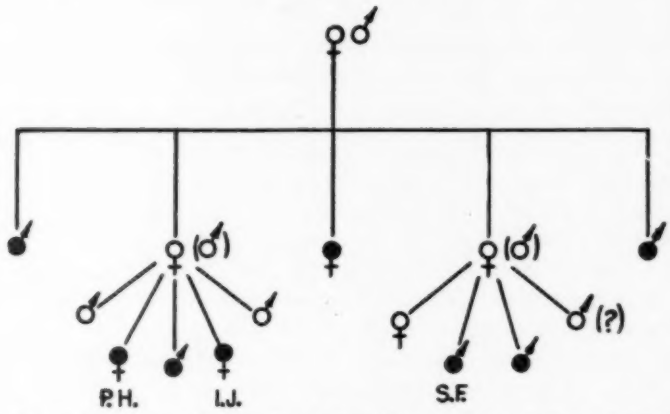

Chart 1.—The family which includes both patients. The black figures indicate involved persons. No individual could be recalled above the horizontal line who was affected with this disease.

The patient was seen again in the clinic on Oct. 30, 1934, at which time it was learned that his intolerance to heat had improved, but perspiration still had not been observed. The degree of nasal obstruction was as marked as before.

When he returned to the clinic on May 15, 1941, he was about 11 years of age. Swimming had been most responsible for relief from heat discomfort. His record in school was very good. At the time of this observation, he was 56 inches tall, and he weighed 94 pounds. His temperature was 100.6° F., rectally, and his blood pressure was 130 mm. of mercury systolic and 75 mm. of mercury diastolic. The skin was dry and there were scattered papular lesions. The only body hair present was situated on the scalp, and this hair was scanty. The frontal bones were prominent, and the nasal bridge was depressed. The lips were thick and protrusive (Fig. 1). The mucous membranes of the mouth and nose were dry, and moderate nasal crusting was present.

Fourteen teeth were present, eight in the maxillary arch and six in the mandibular arch. All the teeth were conical in shape. Roentgenograms revealed one mandibular molar and two mandibular incisors that were forming but were as yet unerupted, making a total of seventeen teeth (Fig. 2). Moderate tonsillar hypertrophy was noted as well as a mild degree of cervical lymphadenopathy.

P. H. was first seen in the pediatric clinic, University of Iowa Hospitals, on May 22, 1938, at which time she was 11 months of age, and the entrance complaint given was "intestinal upsets." Normal in all respects at birth, she was said to have weighed 6 pounds at that time. Her development had been normal with the exception of delayed dentition. She had evidenced feeding difficulty from a comparatively

early age, and vomiting had been frequent. Three weeks prior to admission she began to have a high fever and a cough associated with the vomiting. Pneumonia was suspected.

The child's temperature was 100.4° F., rectally, and her weight was 16 pounds. There was a scattered papular rash over the body. Some prominence of the frontal bones was seen as well as almost complete closure of the anterior fontanel. The buccal mucosa appeared normal, but no teeth were in evidence. The scalp hair was scanty.

Fig. 1.—The full profile of S. F. Note scanty hair and protrusive lips.

The patient was admitted again on July 5, 1940, this time to the isolation service because of measles and pertussis (Fig. 3). About May 15, 1940, she had developed a mild respiratory infection associated with weakness, pallor, and anorexia. The cough continued until the time of admission and was paroxysmal in type. On

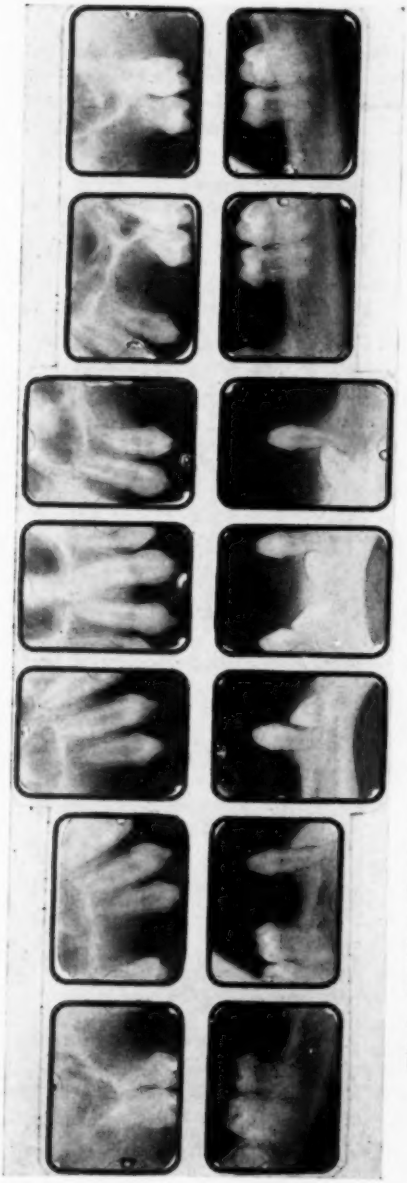

Fig. 2.—Dental roentgenograms of S. F., showing dental dystrophy. No permanent tooth was ever extracted.

Fig. 3.—Patient P. H. when 3 years of age.

Fig. 4.—The primary teeth of P. H. when she was 3 years of age. Note the constriction toward the morsal surfaces.

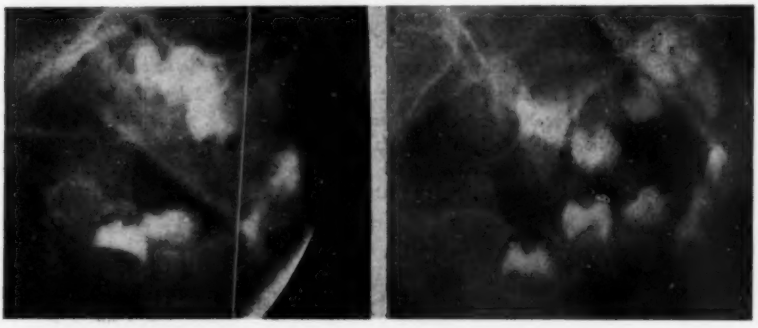

Fig. 5.—Roentgenograms of the right and left mandibular areas, respectively, of P. H. The unerupted first permanent molars resemble "mulberry" molars of congenital syphilis.

June 25, fever developed which reached 103° F., and the mother noted an irregular red rash over the face. Vomiting had been constant. Physical examination showed her to have a generalized blotchy, irregular, maculopapular rash. The tonsils were enlarged and injected, and a moderate degree of cervical lymphadenopathy was found. The blood pressure was 110 mm. of mercury systolic and 80 mm. of mercury diastolic. The blood Wassermann test proved negative.

The dental examination revealed only six teeth to be present, two primary molars and one primary incisor in the maxillary arch, and two primary molars and one primary incisor in the mandibular arch. Roentgenologic examination of the jaws showed the first permanent molars to be unerupted and of abnormal shape; that is, constricted toward the morsal surface. The incisors also were conical in contour (Fig. 4). The dental deformity was similar to that seen frequently in syphilitic dental dystrophy (Fig. 5).

Fig. 6.—Patient I. J. Note scanty hair and protrusive lips.

I. J. was 11 years of age at the time of her last examination in the pediatric clinic, University of Iowa Hospitals, on June 4, 1941. Heat intolerance had been denied. Except for mental retardation of a moderate degree she had developed well.

Her height was 59.7 inches, her weight was 81 pounds, and her temperature was 99° F. The hair was scanty and in evidence only on the head. Moisture was present on the face, in the axilla, and in the inguinal areas. The patient was emotionally upset at the time of examination and tears were present. The frontal bone prominence, saddle nose deformity, and atrophic rhinitis were absent (Fig. 6).

There were nine permanent teeth and one primary tooth in the mandibular arch and thirteen permanent teeth in the maxillary arch. The patient denied having had teeth extracted. Dental roentgenograms revealed that all the teeth which this girl possessed, except the third molars in both the mandibular and maxillary arches, had erupted. The total number of missing permanent teeth was seven (Fig. 7). The severe degree of dental dystrophy shown in Figs. 1 and 4 is not evidenced in this patient. However, the anterior teeth, both maxillary and mandibular, are not of normal contour (Fig. 8).

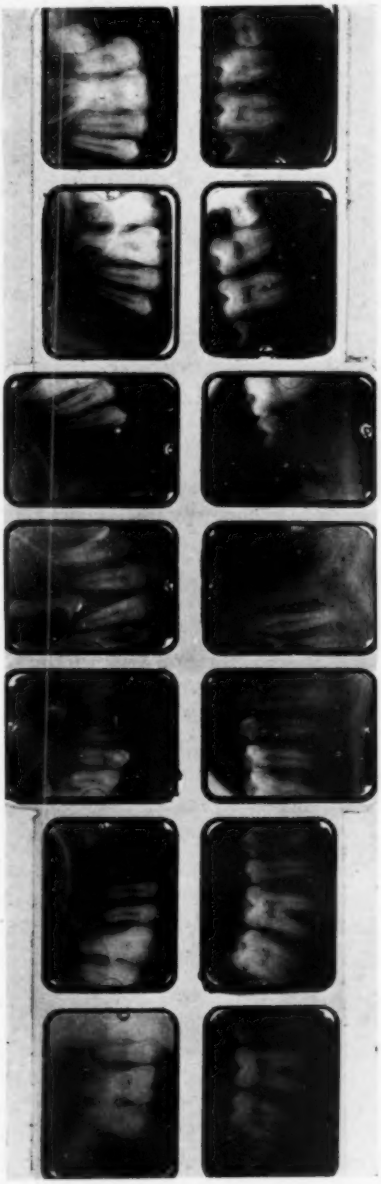

Fig. 7.—Dental roentgenograms of I. J. Note right bicuspid area of the mandible and lateral incisor areas of the maxilla and that teeth are missing in anterior region of mandible.

From the comparison of degree of anodontia shown by the three patients, pouching of the lips being present in all, it is apparent that lack of teeth alone is not responsible for lip protrusion.

Fig. 8.—The anterior teeth of I. J. Note the conical contour.

COMMENT

More than 100 years have elapsed since the first report was made of hereditary ectodermal dysplasia of the anhydrotic type. Rinvik and Syrrist[2] estimate that up to the time of the writing of their paper probably twenty-five true cases had been reported. Since the diagnosis made in many instances was not confirmed by roentgenologic methods, it is not possible to review the literature accurately.

When one considers the incidence of the disease in females, its rarity is even more striking. The characteristic of inheritance of hereditary ectodermal dysplasia of the anhydrotic type is predominantly but not strictly sex-linked, since it does occur in the female. Whether the incidence is dominant or recessive in type cannot be definitely stated, but it would appear that in the family reported here the occurrence was irregularly dominant.

Concerning these patients, the authors were unable to elicit any information which would carry the disease back beyond the siblings of the mothers of these individuals. The two mothers lacked any evidence of ectodermal imperfection. It is quite incredible that these two mothers married men who were "carriers" of the disease. The history, as given by the parents of these patients, would lead one to believe that the mothers were "carriers" and that the family members were involved in a dominant but irregular way. Unfortunately the paucity of family history leaves much to conjecture.

SUMMARY

A report is made of two children who have hereditary ectodermal dysplasia of the anhydrotic type and of a third child who shows only anodontia and alopecia of this syndrome. The three children are closely related. The two children with the complete syndrome are first cousins; the child with the partial syndrome is a sister of one of the two children with the complete syndrome. Siblings of the two mothers are affected; however, the two mothers are normal. It is probable that the disease was transmitted through a maternal carrier state.

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HODGKIN'S DISEASE IN AN INFANT

Report of a Case With a Peculiar Peripheral Blood Picture

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IT IS generally agreed that the lymphomatoid diseases[1] are very closely related. The majority of cases of these diseases can be placed in one or another category and sharply separated from the other members of the group, but occasionally such a separation cannot be made or can be made only at autopsy.[2, 3, 4, 5] The present report deals with a similar case. For a number of weeks the diagnosis was in doubt, and even after the correct diagnosis of Hodgkin's disease was made from biopsy, the blood picture continued to suggest an atypical form of leucemia.

Hodgkin's disease is extremely rare in infants. In 1934 Smith[6] reported on 23 cases of the disease which had been observed at Ann Arbor and an additional 85 cases collected from the literature. In this group there are 5 cases under 1 year of age, 3 of which had the cervical type of the disease, 1 in which the thymus was considered to be the site of origin, and 1 in which the mother died of the disease 1 week after confinement. Rogatz[7] reported a pleomorphic cell lymphosarcoma of the thymus in a 2½-month-old female infant which possibly might be considered as Hodgkin's disease. We have been able to find only two other cases which occurred in infants; one described by Branch[8] and one observed by Chiari.[9] The latter case is cited by Branch from a personal communication. In both cases the mother had demonstrable Hodgkin's disease before the birth of the child. As far as we can determine, then, only 8 cases have been reported in infants under 1 year of age, of which 3 were congenital, 2 thymic, and 3 of the cervical type.

The present case is reported because: (1) it had the characteristic picture of Hodgkin's disease of the abdominal type with a very rapid course, although the patient was only 4 months of age when the illness began. It is apparently the first case of this type to be reported in a child less than 1 year old. (2) This case was not congenital as the baby was examined ten days after birth and was found to be normal in every way. Moreover, the mother has since given birth to another child and repeated physical examinations of the mother and of this second child have shown no evidence of the disease. (3) The patient was a female, and it is said[10] that 75 per cent of all cases of Hodgkin's disease in children occur in males. (4) There was a peculiar peripheral blood picture, which closely resembled that found in leucemia.

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CASE HISTORY

This white baby girl (Albany Hospital, No. 54701) was born Nov. 28, 1938, and weighed 7 pounds. She was a perfectly normal infant, breast fed, and regained her birth weight by the tenth day. Both parents were born in America of Germanic stock; the family history is noncontributory. Up to the time of admission, this patient had had no infectious diseases, no vaccinations, and no immunizations.

On April 4, 1939, the patient was admitted to the Pediatric Service of the Albany Hospital. The present illness had begun one week before with symptoms of a head cold and cough, daily fever to 101° F., with anorexia and constipation.

On admission this 4-month-old baby weighed 10 pounds and was obviously acutely ill. The temperature was 99° F.; pulse, 140; respirations, 44 per minute. Physical examination revealed a well-developed, poorly nourished white female, markedly anemic, coughing and crying weakly. The percussion note was essentially normal, but auscultation showed areas of moist râles throughout the chest. The abdomen was moderately distended but not tender. The liver edge could be felt one finger's breadth below the costal margin. The spleen was markedly enlarged, extending to the umbilicus, was moderately firm, and the notch was easily palpable. It was freely movable in all directions. No lymph nodes could be palpated, no petechiae were present, and the remainder of the findings on physical examination were all normal.

Laboratory Findings on Admission.—The Wassermann test, urinalysis, tuberculin test 1:1,000, and a stool examination for ova and parasites were negative. Radiographs showed no definite evidence of pneumonia. Blood examination showed hemoglobin, 48 per cent; red blood cells, 2,900,000; white blood cells, 25,400. A differential count, made from a blood film stained with Wright's stain, showed segmented neutrophiles, 12; stab forms, 15; metamyelocytes, 2; neutrophilic myelocytes, 1; eosinophiles, 1; basophiles, 1; monocytes, 12; small lymphocytes, 35; large lymphocytes, 5; unidentified cells, 16. While counting 100 white blood cells, 4 normoblasts and 58 smudges were encountered in the smear. The "unidentified" cells were 13 to 14 μ in diameter with a fine chromatin reticulum and pinkish parachromatin in the nucleus. The nuclei were large in proportion to the cytoplasm and many of them contained nucleoli. The cytoplasm was intensely basophilic. These cells were obviously lymphocytic, and a diagnosis of lymphocytic leucemia was considered.

Hospital Course.—The day after admission the baby was given a transfusion of 100 c.c. of citrated blood, repeated on the following day. She gained in strength, the temperature came down to normal, and the cough improved. At the same time, the liver decreased in size until on April 13 it was barely palpable, though the spleen remained enlarged. On this day, the temperature again began to rise, the child coughed frequently, and coarse râles were heard in both bases. The patient was given a total of 13 Gm. of sulfapyridine on April 13 and 14. The white blood count, however, fell to 4,850 cells, and this medication was discontinued.

On April 22 one of the right inguinal nodes became palpable, and by April 24 there were discrete, nontender nodes in both axillae and both inguinal regions. The anterior cervical nodes were also discretely palpable but smaller. The liver and spleen had increased in size (Fig. 1). The total white count was now 5,400. Radiographs taken at this time showed extensive elevation of the periosteum of the humeri, radii, ulnae, and femora. No definite joint swelling was visible.

Because of continued difficulty in making the routine differential blood counts, a supravital examination of the blood was made. The supravital differential count was as follows: neutrophiles, 16; neutrophilic myelocytes C, 1; eosinophiles, 0; basophiles, 0; monocytes, 6; small lymphocytes, 27; intermediate lymphocytes, 7; abnormal lymphocytes, 29; large normoblasts, 12; small normoblasts, 2. The abnormal lymphocytes were rather similar to those described by Tompkins and Cunningham[11] as characteristic of acute lymphatic leucemia.

The patient continued to be anemic despite all attempts at therapy, so that more transfusions were necessary. On May 15 the child's temperature rose to 102° F., unexplainable by physical examination, which lasted for several days.

By May 22 the liver and spleen were larger than they had previously been, the nodes were growing in size, and the child became lethargic and refused its feedings. A chain of axillary lymph nodes were removed on this day for biopsy, from which the correct diagnosis was finally made.

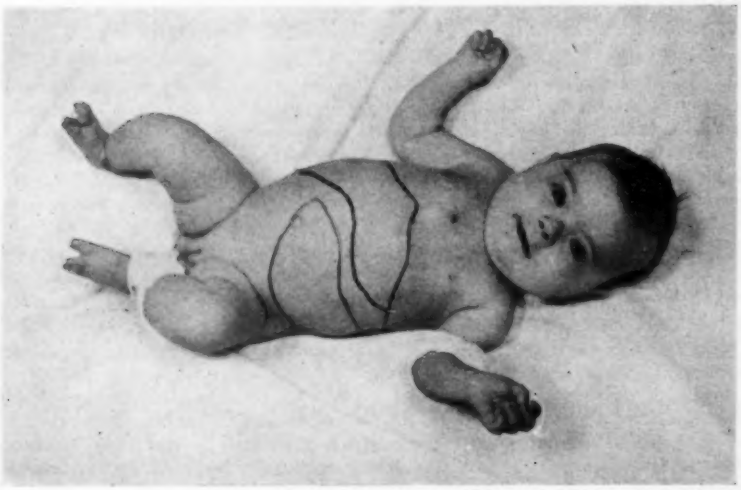

Fig. 1.—The patient on April 26, 1939, showing the outlines of liver and spleen.

Radiographs taken at this time revealed what appeared to be extensive ossification in the periosteal elevations along the shafts of both humeri, radii, ulnae and both femurs and tibiae (Fig. 2).

From May 24 to May 29 the temperature, which had been normal again, rose to 104° F. and respiration became labored.

The child became irritable and progressively weaker. She seemed to be in pain and cried when handled or fed. The abdomen was tremendously enlarged. The liver could be felt at the umbilicus, the spleen considerably below it, and both organs were now tender to pressure. The patient died on June 1, 1939.

Autopsy.—The body was that of a fairly well developed but poorly nourished 5-month-old white female, weighing 12 pounds, 4 ounces. The liver and spleen were palpable just above the umbilicus. No fluid wave could be demonstrated. There were enlarged firm lymph glands in the anterior cervical chain, axillae, and both inguinal regions, and on opening the abdomen enlarged retroperitoneal nodes were seen along the aorta and both iliac arteries.

The pleural and pericardial cavities, mediastinum, heart, most of the gastrointestinal tract, adrenals, ureters, and bladder showed nothing of note.

The lungs were normal in shape, and the lower lobes were moderately congested. Minute pearly foci were present on the surface and were found scattered diffusely throughout the organ on sectioning with the knife. In histologic sections, these were found to consist of aggregations of cells with large vesicular nuclei, plasma cells, eosinophiles, and occasional large multinucleated giant cells and early evidence of fibrosis.

The spleen was greatly enlarged and weighed 130 Gm. and was of a uniformly firm consistency. On section the cut surface presented a reddish pink glistening appearance, which suggested that the spleen was undergoing diffuse infiltration by a neoplasm. Microscopically the outstanding change from normal was the reduced number of lymphocytes and the diffuse overgrowth of fibrous tissue. Only a few splenic corpuscles could be recognized (Fig. 3). Great numbers of cells with large vesicular nuclei were found. Some of these had the characteristics of the Reed-Sternberg cells of Hodgkin's disease, while others were too primitive to identify. A few plasma cells, giant cells, and eosinophiles were found. Nucleated red blood cells were also present. The spleen as well as the lungs was therefore involved in a diffuse tumor of neoplastic nature.

Fig. 2.—Radiograph of the legs taken May 22, 1939, showing extensive ossification in the periosteal elevations on the femora.

There was a large, oval-shaped mass of neoplastic tissue just beneath the muscularis mucosae in one part of the stomach which extended into the muscle coats with much destruction of these layers, but there was no invasion of the mucosa (Fig. 4). Histologic sections of the duodenum also showed large circumscribed masses similar in structure to the one in the stomach beneath the muscularis mucosae, but the muscle layers of this organ had been entirely replaced by tumor tissue. Large numbers of endothelial-lined spaces containing tumor cells were present, and it is believed that these were the regional lymphatic channels.

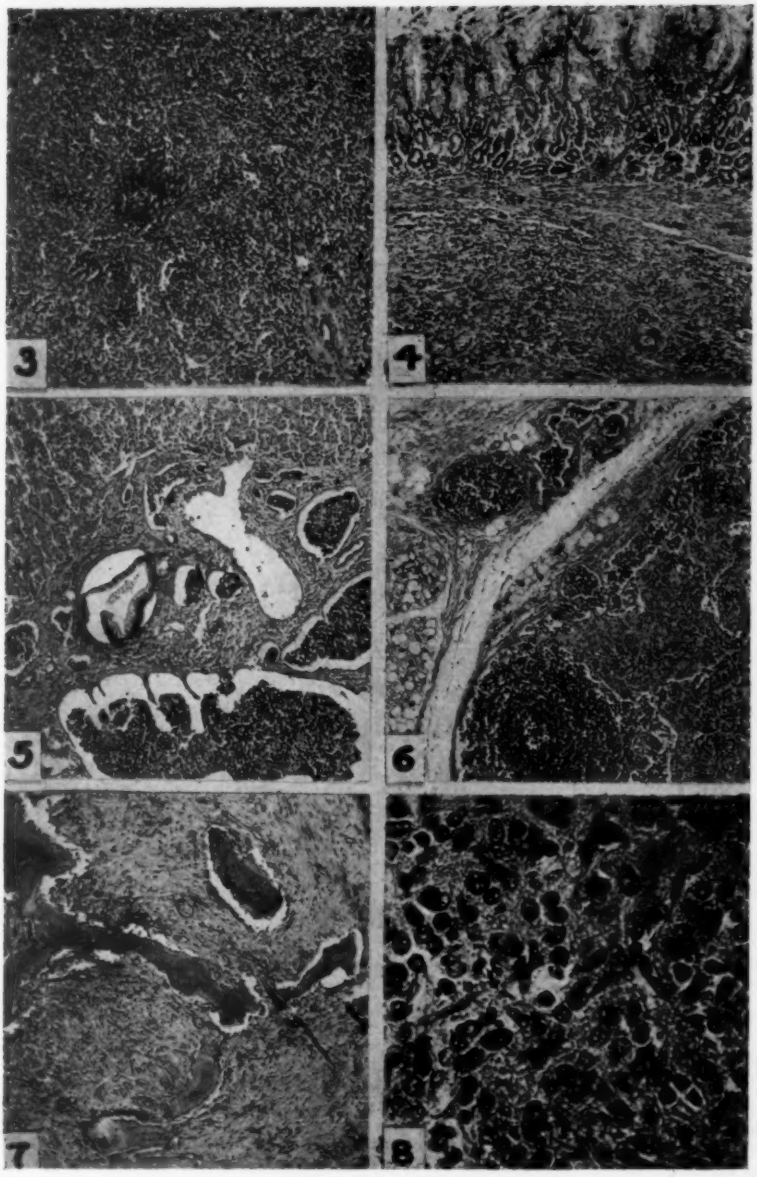

Fig. 3.—Section of the spleen, with a small splenic corpuscle surrounded by neoplastic tissue.

Fig. 4.—Section of the wall of the stomach. Note that the invading cells have not entered the mucosa which is at the top of the picture.

Fig. 5.—Invasion of the periportal lymphatics of the liver by neoplasm. A bile duct is visible in the left center, and normal liver tissue is present at the top.

Fig. 6.—Section of a pancreatic lymph node. The normal architecture, except for the lymph nodule at the bottom of the picture, has been replaced by fibrous neoplastic tissue. Note the invasion of the marginal sinus and the lymphatics in the adjacent connective tissue by the tumor cells.

Fig. 7.—Section of the body of a vertebra. The marrow cavity is completely filled by dense fibrous tissue.

Fig. 8.—High-power photomicrograph of the tumor tissue in a lymph node showing the variation in the size of the nuclei of the neoplastic cells.

The pancreas was deeply imbedded in a mass of neoplastic tissue in the retroperitoneal region. Microscopically it was seen that the normal architecture of the peripancreatic lymph nodes was completely gone and the number of cells greatly reduced, and there was a profuse overgrowth of fibrous tissue. The same abnormal cell types were present. The tissue of the pancreas was being invaded from the adjacent nodes. The lymphatics of the region were markedly dilated and filled with tumor cells.

A mass of neoplastic tissue, continuous with the retroperitoneal tumor in which the head of the pancreas was embedded, extended into the hilum of the liver.

The liver was enlarged and weighed 360 Gm. The capsular surface showed irregular areas of pale yellowish discoloration. The organ was firm in consistency. The tumor mass at the hilum, referred to above, extended upward along the extrahepatic bile ducts, and, when the liver was sectioned, could be traced along the main branches of the biliary tree as a pinkish-yellow, firm, friable tissue resembling the neoplastic growth found in other locations. Microscopically, the portal canals were extensively involved, and from this site neoplastic tissue had spread out into the adjacent liver tissue. Large areas of parenchyma had been replaced. There were several foci of marked fibrous overgrowth containing very few cells. The lymphatics of the portal canals were greatly enlarged and filled with metastases (Fig. 5). The hepatic cells themselves were the seat of albuminous degeneration and fatty metamorphosis. There were numerous areas showing small bile thrombi, and bile pigment could be detected within the liver cords. The gall bladder was thick walled and also infiltrated with tumor tissue.

The pelvis of one kidney contained a large mass of neoplastic tissue which compressed the artery and vein and reduced the ureter to a slitlike opening. In one place this mass of tumor tissue was invading the kidney parenchyma. The epithelial cells of the convoluted and collecting tubules of both kidneys showed marked parenchymatous degeneration.

Lymph nodes from the retroperitoneal, cervical, axillary, and inguinal chains all showed the same changes: almost complete replacement with primary malignant neoplasm, loss of normal architecture, fibrosis, decreased numbers of lymphocytes, and increased numbers of immature "lymphoblastic" tumor cells and giant cells (Figs. 6 and 8).

The bone marrow of the vertebrae was scanty and pale pink in color. Imprints made from it had only very occasional marrow cells and tumor cells present. The cut ends of the ribs and sternum presented a dry, white, fibrillar, honeycombed appearance grossly, and imprints from them contained nothing except a few red blood cells. Microscopic examination showed that the marrow was completely replaced by a dense fibrous tissue (Fig. 7). In some sections, the marginal bone was eroded and continuity established between tumor in the marrow cavity and tumor tissue in the periosteal muscle.

Permission for a complete autopsy could not be obtained, and the condition of the marrow in the long bones and the histology of the changes in the periosteum therefore could not be studied.

Hematology.—During the week following admission the total leucocyte count fell from 25,000 to 4,900. It remained low for about ten days and then began a gradual rise but never became higher than 12,500. Nucleated red cells were present at all times, their number varying from 300 to 1600 per cubic millimeter. Neutrophilic myelocytes were always present in the films, but their number never exceeded 5 per cent of the total count. Eosinophiles were present in normal numbers. The number

of monocytes was slightly increased, but the cells were qualitatively normal. The great majority of the normal lymphocytes in the blood were of the small variety, and only a few were of intermediate size.

The number of lymphocytes was between 50 and 60 per cent of the total white count. Of 6,400 lymphocytes per cubic millimeter on April 24, 5,000 were of an abnormal type, which will be described below. The number of abnormal lymphocytes declined however so that on May 24 only 1,680 out of 7,450 lymphocytes per cubic millimeter were abnormal. A lymphocytosis is considered a characteristic finding in Hodgkin's disease by some authors, but by no means by all.[10]

With supravital staining, the abnormal lymphocytes were 12 to 15 μ in diameter. Their cytoplasm had a yellowish color. The nuclei were large in proportion to the cytoplasm, round or oval in shape, and the chromatin network was too fine to be visible by this method of study save in the cells which contained nucleoli. The neutral red vacuoles were small and numerous and were scattered over the nuclear membrane, to which they were apparently adherent. A few of the cells had a small rosette of neutral red vacuoles in the cytoplasm; these cells had fewer vacuoles attached to the nuclear membrane than cells without the rosette. The mitochondria were peculiar in that their outlines became fuzzy and the dye faded out within half an hour of the beginning of observation with the microscope. These preparations were stained with pinacyanole, and with this dye mitochondria normally remain stained for a long time.[12]

The cytoplasm of these abnormal lymphocytes was very fluid and the cell membrane extremely delicate. The cells would send out thick pseudopod-like processes and begin to disintegrate after being in the supravital film for one hour, even though the slide was not put into the incubator. Most blood cells under similar conditions will remain in good condition for several hours. The fragility of these cells is the explanation of the enormous number of smudges found in the dried smears.

In supravital preparations, normal lymphocytes have less than ten neutral red vacuoles, and the mitochondria are large.[14, 15] In most cases of acute lymphatic leucemia, however, definite changes can be seen in lymphocytic cells.[11] The neutral red vacuoles increase in number and sometimes stain a deep blackish red color, indicative of increased acidity. The mitochondria increase in number and show a definite decrease in size. The presence of such cells in the peripheral blood of the present case, as well as the presence of lymphocytic cells containing nucleoli in the smears stained with Wright's stain, might have led to a diagnosis of leucemia, if the biopsy had not been done. The occurrence of these abnormal lymphocytes in the present case of Hodgkin's disease is taken as further evidence of the close relationship of this disease to lymphocytic leucemia.

This patient had no petechial hemorrhages or purpuric spots visible at any time during the course of the disease, nor was there ever any evidence of internal bleeding. A platelet count on May 29, three days before death, showed 226,000 per cubic millimeter by the direct method. Nevertheless, many of the blood platelets were qualitatively markedly abnormal. Many of them were of giganitc size (up to 13 μ in diameter) and in the supravital preparations at first glance resembled erythrocytes containing no hemoglobin. Closer examination, however, showed that they had a clear, nonfluid exoplasm and an endoplasm containing fine neutral red vacuoles and mitochondria, just as normal blood platelets do on a smaller scale. In some the cytoplasm was yellow, in others colorless. Because of their fragility, these abnormal platelets often assumed bizarre shapes. Similar abnormal blood platelets have been described in Hodgkin's disease by Bunting.[13]

SUMMARY

1. A case of acquired Hodgkin's disease of the abdominal type with a rapid course in an infant 4 months old is described.

2. The peripheral blood contained an abnormal type of lymphocyte which might have led to an erroneous diagnosis of lymphocytic leucemia.

3. The presence of this type of lymphocyte in the blood is taken as further evidence of the close relationship between this disease and lymphocytic leucemia.

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HEREDITY AND GENETICS

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THE belief that nothing practical is known about human heredity, except that red hair and hemophilia run in families, has been too prevalent among the public and unfortunately among the medical profession also. Not only is much known of medical genetics, but the knowledge is of practical value in the diagnosis and prognosis of disease and in the everyday practice of medicine. For example, in addition to the valuable advice which can be given to prospective parents with a poor heredity on the inadvisability of having children, mothers who have had one abnormal child should be told whether subsequent ones may also be malformed. Physicians who are interested in the genetic aspects of the family histories of their patients can be on the alert for the development of certain diseases and during the early, usually overlooked stages, can start treatment which may prevent disastrous consequences. A knowledge of heredity may also be applied in medicolegal cases. Furthermore, the careful compiling of family histories by physicians will help geneticists to clear up the mode of inheritance of some of the more obscure conditions.

The variance of human mental and physical traits, as well as the occurrence of diseases, is due partly to genetic variations and partly to the exigencies of the environment. The latter also may modify the expression of a hereditary factor. The constitution inherited from his parents often may be responsible for a child's being underdeveloped both physically and mentally. Although exceptions occur, tiny parents cannot be expected to produce giants, nor morons geniuses. However, nutritional and mental guidance may improve the population. The widespread knowledge of these latter factors probably is responsible for the fact that growth, especially during the first year of life, is greater in infants who have adequate medical supervision, and that the average student entering a university at present is two inches taller and seven pounds heavier than during the last generation. In addition to the structural and physiologic characteristics peculiar to members of certain families, a number of definite defects and malformations are hereditary.

Generally speaking, each hereditary characteristic of the individual is dependent on a pair of genes, one of which was received from each of his parents. If the pair of genes for a given characteristic are alike he is said to be homozygous for this trait, and the gene which he hands

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on to each of his children will be the same (barring mutation, which is a sort of genetic accident changing the gene itself). If, however, one of the genes is not like the other, the individual is said to be heterozygous in respect to this trait. In this case there are two main possibilities: Either one trait will be dominant over the other, masking its effect, or the two will blend. In the case of the homozygous individual, the genotype (the hereditary make-up, as given above) and the phenotype (the appearance) are to all intents and purposes the same. However, in the heterozygote the phenotype will give evidence of the dominant gene only, unless it is a case of blending, which is comparatively rare. Without the test-crossing which is used in plant and animal breeding, it is quite difficult to distinguish between the individual who is homozygous for the dominant gene and one who is heterozygous. In human pedigrees, data must usually be collected from several families showing the same trait, and then the frequency and distribution of its occurrence must be mathematically analyzed.*

According to mathematical probabilities, in the offspring of two heterozygous parents three will show evidence of the dominant gene, while only one (homozygous for the recessive gene) will show the recessive trait. Of the three who show the dominant trait, one will be homozygous and the other two will be heterozygous, carrying one dominant and one recessive gene each. Thus, if it is desired to rid the population of an undesirable dominant trait, it will be sufficient to persuade all individuals who show it to refrain from having children. This is a comparatively simple problem. The real difficulty comes when an undesirable trait is recessive. If a child shows such a trait, while his parents appear normal, this is an indication that the parents are both heterozygous, each carrying one recessive gene which does not show up in them because the dominant normal one is also present. In such a case these parents should be warned that further children may also show the trait. Further, in case the disability is unimportant it will be sufficient to warn the normal siblings of the affected child against marrying into families in which the anomaly is known to occur. In cases where the affliction is serious and frequent in the population, all the siblings should be warned against having children, since two out of three of the normal ones will be heterozygous, carrying the recessive gene and capable of reproducing the anomaly in the next generation if their mates happen also to be heterozygous.

Sex-linked heredity is a little different from the foregoing types. The chromosomes which carry the sex-determining genes carry also a number of other genes, those which determine the possibility of hemophilia and red-green color blindness among them. Most of these genes are carried on the X-chromosome. When there are two X-chromosomes present, the individual is female; when only one is present the indi-

*For further information on this and other points, see also Snyder, Laurence H.: The Principles of Heredity, ed. 2, New York, 1940, D. C. Heath & Co.

vidual is male. The Y-chromosome, which in the male forms a partial complement to the single X-chromosome, is inherited from the father and is much shorter than the X-chromosome, lacking many of the mates to the X-chromosome genes. Thus girls have complete pairs of genes of the sex-linked sets and may be either homozygous or heterozygous, while males have only one of each pair of genes and these they can pass on only to their daughters in the X-chromosomes. Their genotypes and phenotypes are identical since they are obviously homozygous.

TABLE I

CONDITIONS DUE TO RECESSIVE TRAITS

Albinism	Ichthyosis fetalis (e)
Amaurotic family idiocy	Icterus gravis (f)
Amyotonia congenita	Infantile muscular atrophy
Blood group O	Keratoconus
Clubfoot	Megalocornea (a)
Color blindness (a)	Merzbacher-Pelizaeus disease
Congenital hydrops	Microcephaly
Cryptophthalmos	Microcornea (a) (d)
Day blindness (a)	Microphthalmos (a) (d)
Deaf-mutism (c)	Morquio's disease
Diffuse cerebral sclerosis	Niemann-Pick disease
Ectodermal dysplasia (a) (d)	Oguchi's disease (a) (d)
Enuresis	Ochronosis with alkaptonuria
Erythroblastosis	Phenylketonuria
Exophthalmic goiter	Porphyria
Gaucher's disease	Progressive lenticular degeneration
Hemophilia (a)	Progressive muscular dystrophy (a)
Hand-Schüller-Christian's disease	Retinal detachment (a) (d)
Hereditary spastic paraplegia (d)	Retinitis pigmentosa (a) (d)
Hurler's syndrome	Schilder's disease
Hydrophthalmos	Spina bifida
Hypertrophic neuritis	Tay-Sachs disease
Ichthyosis congenita (e)	von Gierke's disease

(a) Sex-linked trait; (b) sex-influenced trait, dominant in men (40 per cent), recessive in women (7 per cent); (c) two factors (pairs of genes); (d) sometimes dominant; (e) lethal; (f) variable expressivity; (g) good expressivity; (h) poor expressivity; (j) sometimes recessive; (k) unilateral ptosis usually is due to nonhereditary causes; (m) complete penetrance and perfect expressivity; a form involving only the index fingers and second toes has complete penetrance and poor expressivity; (n) high penetrance; (p) low penetrance; (q) dystrophic form also may be recessive; (r) often due to nonhereditary factors; (s) dominant in the white race with low penetrance and poor expressivity; recessive in negroes; (t) antecedent achlorhydria probably is dominant.

In case of very undesirable sex-linked recessive traits, normal males in the family, since they have only the dominant normal gene, can marry with impunity. However, half of their sisters can be expected to be heterozygous and one-half the sons of each of these will show the trait. Of course the male who shows the recessive trait will pass it on to all his daughters, though they will not show it unless they receive a gene for this trait from their mother also.

Blood group heredity is a combination of two types. A and B are both dominant to O but not to each other, blending to form AB when occurring together. Types M and N also blend but without dominance, and are of practical interest only in genetic and medicolegal studies, since they do not produce any transfusion reactions, as do A, B, and O. There is also a new blood factor which is receiving some attention, as

it is thought to be responsible for erythroblastosis. The theory is that when a baby inherits this dominant factor, known as Rh, from its father, while its mother lacks this factor, the mother's blood may hemolyze that of the baby in utero. This study is still, however, in the experimental stage and needs further confirmation.

TABLE II

CONDITIONS DUE TO DOMINANT TRAITS

Absence of patella	Pterygium
Absence of upper teeth (b)	Fragilitas ossium
Achondroplasia (j)	Friedreich's ataxia (j) (p)
Allergy (f)	Glaucoma (n) (r)
Alopecia totalis	Gout (p)
Aniridia	Hemoptysis (non-tbc)
Arcus juvenilis (embryotoxon)	Hereditary cerebellar ataxia (j) (p)
Astigmatism (j)	Hereditary essential tremor
Baldness (b)	Huntington's chorea (g) (n)
Bilateral ptosis (k)	Hypertrichosis
Blood groups A, B, and MN	Hyperopia (j)
Blue sclerae	Hypospadias (p)
Brachydactylia (m)	Hypotrichosis et dystrophia unguium
Cataract	Ichthyosis vulgaris (f)
Cerebellar degeneration (p)	Keratosis follicularis
Coloboma iridis (j)	Keratosis palmaris et plantaris
Congenital dislocation of hip (p)	Lagophthalmos
Corneal opacities (j)	Leucemia (p)
Diabetes insipidus (p)	Lobster claw
Diabetes mellitus (p)	Manic-depressive psychosis (f) (p)
Distichia	Migraine (g) (n)
Dystrophia myotonica (h) (n)	Mongolian spots
Ectopis lentis	Mongolism (p)
Epicanthus	Monilethrix
Epidermolysis bullosa (q)	Multiple cartilaginous exostoses (p)
Epilepsy	Multiple telangiectasis (p)
Erythroblastic anemia	Myopia
Familial hypereosinophilia	Myotonia congenita
Familial hemolytic jaundice (f) (n)	Neurofibromatosis (f) (n)
Familial periodic paralysis (p)	Nystagmus (a) (r)
Ophthalmoplegia (j)	Purpura (p)
Otosclerosis (a) (c)	Renal glycosuria
Ovalocytosis	Sickle-cell anemia
Paralysis agitans (p)	Strabismus (j)
Perceptive deafness	Supernumerary teeth
Peroneal muscular atrophy (a) (j)	Symphalangy
Phlebectasis	Syndactylism
Polydactylism (s)	Tropho-edema
Pernicious anemia (t)	Tuberous sclerosis
Psoriasis (j)	

See footnote to Table I.

The neat and exact pattern of dominance is somewhat confused by the fact that a member of another pair of genes may mask the presence of the one under consideration, and in that case the masking gene is said to be epistatic. The appearance of certain traits is also dependent on what are known as their penetrance (the degree of certainty with which one can count on their showing when the dominant genes which are responsible for them are present) and their expressivity (the stability which they show when affected by other genes or by environmental factors).

TABLE III

CONDITIONS DUE TO SEX-LINKED TRAITS

Color blindness (red-green)	Nystagmus
Ectodermal dysplasia	Oguchi's disease
Hemophilia	Otosclerosis
Leber's disease (familial cerebro-macular degeneration)	Peroneal muscular atrophy
Megalocornea	Progressive muscular dystrophy
Microcornea	Retinal detachment
Microphthalmos	Retinitis pigmentosa

See footnote to Table I.

Sex-influenced traits are those in which one gene of the pair is dominant for males and the other for females. Pattern baldness is one of these traits and a form of white forelock described by Holmes is another.

Lethal factors are those which, in a homozygous individual, cause death at a fairly early age, even in embryonic stages. Some of these are due to dominant and some to recessive genes. The reason often given for the rarity of hemophilic females in families where they might be expected is that the existence of two hemophilic genes in the female is probably lethal and they probably do not live beyond the early embryonic stage.

Concordance means the occurrence of the same condition in a significantly higher percentage of identical twins than of fraternal twins. Since genotypes of identical twins are always the same, this information will give a pretty good indication as to whether a condition is hereditary or merely due to family environment.

Sex-limited factors are those which are capable of expression in one sex but not in the other. This expression is believed to be controlled by the sex hormones appearing in early embryonic life, and in turn determined by the sex chromosomes.

Tables I, II, and III are derived from statements in the literature. In addition to the hereditary traits which follow one or more of these methods of transmission, many other conditions probably are hereditary, though their mode of transmission is still unclassified; e.g., aphasia (word blindness and deafness), ateliosis, cleft palate, dementia praecox, epistaxis, fingerprints, harelip, moronity (multiple factors), psychopathic inferiority, schizophrenia, skin color, and syringomyelia. Tumors also have an unclassified genetic basis, because the same type of tumor often occurs in the same organ at approximately the same age in various members of certain families, and especially in identical twins (high concordance); e.g., brain, eye, ovarian, and uterine tumors. Furthermore, certain families have an apparent predisposition to certain diseases, though the immediate cause is environmental; e.g., cretinism, diphtheria, measles, scarlet fever, and tuberculosis. Members of families in which these tendencies occur should be examined frequently and should avoid all known environmental causes of these conditions.

The Pediatrician and the War

The following is a continuation list of Fellows of the American Academy of Pediatrics on active duty in the military services:

Army

Dr. Harry S. Andrews, Louisville, Ky. (Major)
Dr. Frazier Binns, Nashville, Tenn. (Captain)
Dr. Montgomery Blair, Jr., Washington, D. C. (Major)
Dr. William W. Briant, Jr., Pittsburgh, Pa. (Major)
Dr. Sidney S. Chipman, Norwalk, Conn. (Major)
Dr. David H. Clement, Buffalo, N. Y. (Captain)
Dr. Norman T. Crane,* Plainfield, N. J.
Dr. Vincent Del Duca, Camden, N. J. (Captain)
Dr. J. Gilbert Eblen,* Knoxville, Tenn.
Dr. Philip C. Elliot, Nashville, Tenn. (Captain)
Dr. David P. Evans,* East Orange, N. J.
Dr. Merrill W. Everhart, New Orleans, La. (Major)
Dr. Thomas A. Gibson, Winchester, Va. (Major)
Dr. Paul Harper, Bridgeport, Conn. (Major)
Dr. George Heller, Englewood, N. J. (Captain)
Dr. Samuel J. Hoffman, Chicago, Ill. (Major)
Dr. William A. Howard, Washington, D. C. (Captain)
Dr. Howard T. Knobloch, Bay City, Mich. (Captain)
Dr. J. Keller Mack, Louisville, Ky. (Captain)
Dr. Robert J. McGillicuddy, Lansing, Mich. (Captain)
Dr. Russell W. Mapes,* Beverly Hills, Calif.
Dr. John W. Maroney,* Wilmington, Del.
Dr. Henry S. Meyer,* Houston, Texas.
Dr. Masters H. Moore, Lawton, Okla. (Captain)
Dr. E. Harrison Nickman, Atlantic City, N. J. (Captain)
Dr. Edward T. O'Donnell, Wilmington, Del. (Major)
Dr. Owen S. Ogden, Louisville, Ky. (Captain)
Dr. Daniel J. Pachman, Chicago, Ill. (Captain)
Dr. Marsh W. Poole,* Detroit, Mich.
Dr. H. H. Shuman, Fitchbury, Mass. (Major)
Dr. Harry B. Silver, Newark, N. J. (Major)
Dr. Charles A. Tompkins,* Omaha, Neb.
Dr. Harry A. Towsley,* Ann Arbor, Mich.
Dr. Talbot A. Tumbleson, Beaumont, Texas (Major)
Dr. Robert O. Y. Warren,* Wilmington, Del.
Dr. Thomas S. Weaver, Nashville, Tenn. (First Lieutenant)

Navy

Dr. Harry E. Gerner, Jersey City, N. J. (Lieutenant)
Dr. Bertrand I. Krehbiel, Topeka, Kan. (Lieutenant Commander)
Dr. Alwin C. Rambar, Chicago, Ill. (Lieutenant Commander)
Dr. Willard B. Rew, Yakima, Wash. (Lieutenant Commander)

Dr. Councill C. Rudolph,* St. Petersburg, Fla.
Dr. Byron K. Rust, Indianapolis, Ind. (Lieutenant Commander)
Dr. Jack E. Strange, New Orleans, La. (Lieutenant Commander)
Dr. Alfred A. Trivilino,* Jamaica, N. Y.
Dr. James H. Wallace, Oak Park, Ill. (Lieutenant Commander)
Dr. William R. Wilson, New Haven, Conn. (Lieutenant Commander)

Canadian Royal Army

Dr. Harry Medovy, Winnipeg, Manitoba (Captain)
Dr. Henry P. Wright, Montreal, Quebec (Major)

Special

Dr. Gilbert S. Osincup, Orlando, Fla. (Senior Surgeon, U. S. Public Health Service, and Chairman of Medical Service, Office of Civilian Defense)

The Editors will receive additional names of Fellows entering the services for future lists.

The Nutritional Care of Children in Wartime†

Julian D. Boyd, M.D., Iowa City

The physician has an important place to fill in the program of nutritional advancement. The community looks to him as a leader in matters relating to health and depends upon him as an interpreter. The physician must be more than a healer of disease; he must share responsibility in the promotion of healthful living. His services may be likened to those of an engineer; his objective is to attain the most efficient functioning of the human machine. In that role, he serves as the keystone in the translation of scientific progress into terms of human welfare. Unless the physician is equipped to perform this function adequately, social advancement is impeded. No other professional worker has the physician's unique opportunity for influencing the public in matters pertaining to physical welfare. In the interpretation of nutritional advances, the medical profession has been handicapped. Workers in biochemistry and in allied fields have been largely responsible for the rapid advances made in the science of nutrition, and their findings have reached the medical practitioner only through devious routes. Great progress in nutrition has been made during the past few years, and application of findings to mankind is essential and unavoidable. It is important that the physician adopt the new knowledge and apply it toward the best interests of his patients and the other members of his community. If he fails to accept in this field the leadership which rightfully should be his, both he and the public will be the losers.

Improvement of the national level of nutrition can do much toward the advancement of our war effort. The current crisis has made it imperative that society operate in an efficient manner. Our democracy is built on the basis of the welfare of each of its citizens; unfavorable conditions in any area will operate not only against the communal welfare, but also to the disadvantage of each of us.

With the coming of war, it has become doubly important that we conserve all our human resources and that each individual be employed as profitably and efficiently as possible. Our concern must be directed not only toward manpower, but toward childpower as well. Our national welfare throughout the coming years will be determined by the well-being of the young men and women who

*No information as to present rank.

†Presentation during Panel Session relating to The Child During Wartime, Cleveland, May 16, 1942.

must carry the load during the postwar period. Their success in this regard will be augmented or handicapped through the health measures employed now during their childhood.

Research has demonstrated that health and efficiency may be advanced or retarded markedly through the nature of one's diet. Recognizing this fact, we as physicians should not be satisfied until we are assured that food is accomplishing all that food can accomplish toward the advancement of health in this country. In the consideration of problems of nutrition in wartime, we must start by questioning the adequacy of nutrition of our citizenry during times of peace. Is there anything to justify us in accepting peacetime nutritional levels as a desirable yardstick for our policy during war?

A few years ago a committee of experts in nutrition made a survey of the status of the inhabitants of the British Isles and reported that disturbances of nutrition were widely prevalent. These findings were contradicted by a committee composed of clinicians appointed by the British Medical Society in response to the challenge of the earlier report. The findings of the one group did not neutralize those of the other: both reflected the confusion of ideas which is prevalent regarding the identity of nutritional deficiency states. More recently, clinicians have conducted studies which have revealed faults of nutrition masquerading themselves under a variety of guises. It now is accepted further that the harmfulness of an unsatisfactory regimen may remain latent for long periods of time before manifest or detectable disease appears.

The modern clinician has accepted the concept that animals in the laboratory or on the farm may be conditioned in surprising degree, for better or for worse, through variation of the nutrients supplied to them. Studies have shown that types of physique and of growth, often attributed casually to heredity, are controllable and modifiable through nutritional means. Conditions which formerly were considered to represent the best possible response of the animal have been enhanced through improved feeding practices. Animals have experienced increased rate and degree of growth, enhanced vigor, greater longevity, and heightened resistance to disease. The farmer engaged in stock feeding has profited greatly through these discoveries, and industry similarly has been influenced profoundly. There is no apparent reason why similar benefits should not be expected through the betterment of human feeding. Application of nutritional science to mankind has lagged unnecessarily. Now, however, largely through stimulation of wartime needs, interest is being awakened and conditions are improving steadily.

Controlled nutritional studies with human subjects have shown that man is not essentially different from the lower animals in the nature of his needs or in the pattern of his response. The response of individuals of different ages to diets of varied composition has been observed under conditions of exact measurement, and from such studies conclusions have been drawn as to the most favorable nutritional regimens obtainable for normal body functioning. It has been demonstrated that nutritional requirements may be predicted in terms of age of the subject, his degree of activity, and his stage of development. Deficiency may be demonstrable on the basis of the subject's efficiency of utilization of his intake, yet this deficiency may not be detectable through any simple clinical means. Commonly prevalent conditions, such as mild chronic upper respiratory infection, have been shown sufficient to render inadequate a nutritional regimen which would be ample in the absence of such condition. Imbalance of the diet in certain regards has served to precipitate inadequacy of the diet in other respects. Different individuals under apparently corresponding conditions of health and of diet have been shown to vary in their efficiency of utilization of food; a regimen which has proved ample for the one might be inadequate for

another. As a result of these differences, desirable diets usually are considered in terms of the type of response to be expected from the average individual, with recognition that modifications may be necessary to meet imposed conditions.

It is convenient to classify nutritional levels into various categories. At the lowest level we can place the subsistence diet. This will permit the maintenance of life at an emergency level but will fail to offer suitable protection. Its use does not favor normal growth or functioning, and the subject receiving such a diet is predisposed to primary and secondary deficiency states. Above the subsistence level is recognized a zone which is neither bad nor good, but which is intermediate. This level characterizes the dietaries most commonly employed; they may provide for apparent comfort and well-being yet fall short in varying degrees in meeting all nutritional needs. The ideal level of nutrition is the one which meets all the requisites mentioned earlier. It offers everything that food can contribute toward the subject's well-being. As physicians, it is the optimum level of efficiency with which we should concern ourselves. To accept poorer regimens is to condone imperfect functioning.

When an individual subsists on an imperfect diet, his body is forced to adopt the most favorable compromise possible under the existing circumstances. With outstanding specific deficiency, the well-recognized deficiency diseases will tend to develop: rickets in the infant, osteoporosis in the older subject, scurvy, beriberi, xerophthalmia, and pellagra. With milder and less specific deficiencies, the compromise may manifest itself in a variety of forms. Masked malnutrition is common. It easily is overlooked. Probably many of the patients a physician sees each day have masked malnutrition, and with the usual casual examination its presence and significance are not suspected. We may excuse poor physique, small stature, or faulty posture as matters of heredity or of constitution; yet if the subject with any of these traits were to be placed under a desirable nutritional regimen during his period of development, his physique and response might become normal. Constipation is widely prevalent; with the exception of a few instances, constipation in itself may be accepted as an index that the diet is not as it should be. The same may be said with regard to decay of teeth. Tooth decay is one of the commonest types of abnormality encountered among our patients; it frequently is manifest by the time the child is 2 years old.

Any physician who has witnessed controlled studies with children whose diets have been improved above the prevalent level will substantiate the following dictum: Dietary supervision can lead to improved health and vigor in children who initially did not appear grossly ill or malnourished. The manifestations of improved nutrition are many. In the State University of Iowa we have been interested especially in the lessening of tooth decay in children who for years have been under therapeutically prescribed dietaries because of metabolic disturbance. With an intake which is designed to meet all nutritional needs in an optimum manner, the incidence of tooth decay in such children over periods of several years has been negligible. Collaterally, the general level of health in these children has been much better than in the average child of similar socioeconomic level.

Recently the Committee on Foods and Nutrition of the National Research Council has codified current knowledge regarding nutritional needs and has published its conclusions in tabular form. The table deals with the quantitative need for specific nutritional factors for persons of all ages. The information so presented becomes more usable when it is translated into terms of commonly available foodstuffs and the amount of each needed to assure a diet adequate in all regards. When this is done, it becomes apparent that all requisites for good nutrition can be supplied through the use of easily available foods, if we properly include fish liver oil among the foods rather than considering it as a pharma-

ceutical agent. Such a diet includes the following ingredients in each day's intake, expressed in terms of need of the school child: one quart of milk; one or two eggs; one serving of lean meat; two liberal servings of leafy or root vegetables, one preferably uncooked; two liberal servings of fruit, one of them raw, preferably citrus; one teaspoonful of fish liver oil (400 to 800 units of vitamin D); and additional foods to meet the caloric needs, which may be cereal products, sugars, or fats. It is advantageous to use whole grain cereal products or those which have been enriched. Excessive amounts of sweets, while probably not harmful in themselves, may lessen the appetite as well as crowd from the diet some of the foods which are valuable because of their mineral or vitamin content.

When a diet similar to the foregoing has been used in its entirety as prescribed, one can be assured that provisions for the body's needs have been met. If any of the prescribed items are omitted or slighted, the amounts of essential nutrients may fall below the desired level. Substitutions cannot be made without incurring the danger that the substitution is incomplete. For example, the omission of milk cannot be compensated merely through the administration of equivalent amounts of calcium in other forms. It is necessary as well to provide additional protein, riboflavin, thiamine, and possibly other diet components in order to compensate fully for the absence of milk.

The dietary regimen just described is simple, and at first glance many parents will assure the physician that their child is eating essentially what has been listed. When one studies the diets actually consumed by individual children, or by broad segments of the child population, the intake is found to fall significantly below that which is desirable. Many, if not most, of the prescribed ingredients are used in amounts which are insufficient to meet the purpose for which they are included. This is true in terms of the level of consumption of milk, vegetables and fruits, fish liver oil, and oftentimes, meat. As a consequence, the average child's diet frequently is deficient in its content of vitamins D, C, and B complex and in calcium, protein, and iron. Often it is so low in its content of succulent unabsorbable waste that constipation is to be expected. If the recommendations of the National Research Council are valid, the majority of children in this country are subsisting on diets which are poorer than are needed for adequate nutrition.

The correction of poor diets does not lie in the use of vitamin or mineral concentrates. Any attempt at such reinforcement of the diet usually will be incomplete in some regards and will tend to direct undue emphasis toward certain components to the neglect or oversight of others. Food needs are best met through the use of foods rather than through pharmaceutical products.

The evidence presented substantiates the claim that the nutritive state of United States children as a group has not been satisfactory during prewar years. In designing our program relating to nutrition during wartime, should we be concerned with the avoidance of retrogression in conditions as they have been, or instead should we attempt to establish levels necessary for most efficient function? Without improvement of past standards, we may expect the continuance of previous dietary defects. We have been told of the high incidence of dental defects among selective service candidates and the proportion of men considered unacceptable for military service because of poor teeth. Using the same diagnostic criteria employed during the first world war, the condition of the teeth of draftees was poorer during recent examinations than in 1917. Current evidence indicates that the dental defects could have been prevented if the nutritional knowledge now available could have been put into practice during the past twenty years. If within the next decade there is not an outstanding lessening of the incidence of caries, society must hold itself responsible for its continuance.

The problem of improving nutritional levels is one which must be shared by many agencies. The physician must contribute his share both through the employment of suitable nutritional standards for his patients and through the prestige of his opinion in the community. Education is necessary relating to the nature of the problem and how it is to be met. This education must be directed toward medical and other professional groups as well as toward the American family. The national and state nutritional conferences have laid the groundwork for group education, and similar organizations now are carrying on demonstration projects in counties, towns, and neighborhoods. It seems unfortunate that in most areas the physicians of the community have not been assigned any part in these programs. Both the physician and the community at large will be handicapped if this situation is allowed to continue.

To make the educational campaign effective, it must be translated into terms understandable to the public at large. As long as discussion deals with unitage of vitamins or milligrams of essential minerals, it cannot become of practical importance. People should be offered information in terms of the value and importance of easily available foodstuffs and the amounts of various ingredients needed to supply adequate diets. They should be helped to gain such insight that they instinctively will choose foods wisely and have nutritional awareness during every season and at all times. The public and the physician should learn to think of foods rather than of pills and of concentrates when the subject of nutrition is under consideration. Some form of motivation will be necessary. People must come to realize that better eating will pay actual dividends in the form of better health and the lessening of disease.

Numerous agencies and professions will be concerned in the conduct of any adequate nutritional program. It is important that the efforts of each of these be unified. Each agency will serve either to advance or to retard the ultimate effort. Passivity will result in noncooperation and will hinder the program. The physician in his routine practice may carry the realization that most of his patients need and will appreciate specific advice regarding the improvement of their dietary regimen, even though their primary complaint may not be relevant to nutritional problems. Through representation on public boards, the physician may help to safeguard nutritional practices or to improve them.

Certain group efforts are now under way in many communities of the nation. Among these may be mentioned the improvement of school lunches. This is being accomplished in at least three different ways. First, in some schools provisions are being made to supply school children with all or part of the midday meal, the costs being met partly through voluntary payments by the children able to make them, part coming through provision of foods from the surplus commodity list, and part through subsidy from philanthropic organizations. In principle, this plan seems excellent. Second, many communities now supplement the child's home nutrition through supplying a half pint of milk at recess at the cost of one cent, the extra cost being met through federal or other subsidy. This plan too has much to recommend it. Third, efforts are being made to offer more expert supervision of school cafeterias or restaurants, designed to further the use of valuable food products and to lessen the use of substances which offer glamour rather than nutritional worth.

Commercial efforts being made to increase the level of consumption of dairy products fall in line with the objectives of the nutritional program. During the past year the dairy industry in Iowa has sponsored the broadcasting of football games, and the commercial announcements interspersed throughout the play-by-play descriptions have been of desirable nature. Many of the other industries are helping to spread propaganda of a desirable type; the less honorable advertising material is less prominent on the radio and in the magazines than formerly.

The enrichment of foodstuffs with protective factors offers a means of raising the level of nutrition. The addition of vitamin D to milk, and the enrichment of flour with vitamins of the B complex and with iron, are examples.

The program of attack still remains fluid. In summary, however, each of us should recognize that the nutrition of the children of this country must not be left to chance during the war and thereafter. Past levels of nutritional adequacy have not been satisfactory, and damage has resulted which has handicapped us in our war effort. The objective of the current program should be to attain the highest state of efficiency, using improved nutrition as a mechanism toward that end. As physicians, we should accept our fullest responsibility in the interpretation of nutritional needs to our patients and in the furthering of community programs relating to nutrition.

American Academy of Pediatrics

Proceedings

Minutes of the Meeting of the Executive Board of the American Academy of Pediatrics

Chicago, Ill., June 7, 1942

The following were present:

President: E. C. Mitchell
Vice-President: Borden S. Veeder
Secretary-Treasurer: Clifford G. Grulee
Assistant Secretary: Edgar E. Martmer

Regional Chairmen:

Region I, Stanley H. Nichols
Region II, Hugh Leslie Moore
Region III, Lee Forrest Hill
Region IV, Edward B. Shaw

Associate Chairmen:

Region I, Lewis Webb Hill
Region II, Warren W. Quillian
Region III, George F. Munns

The applications for membership were first considered and the following elected to Fellowship:

Region I

Catherine S. Amatruda, New Haven, Conn.
Nina A. Anderson, Philadelphia, Pa.
Barbara Beattie, Littleton, N. H.
Theodore Bennett, Boston, Mass.
Sidney Blumenthal, New York, N. Y.
J. Wallace Cleland, Lansdowne, Pa.
David Hale Clement, Buffalo, N. Y.
Stuart S. Corbin, Burlington, Vt.
Hester B. Curtis, Washington, D. C.
Lee Edward Farr, Wilmington, Del.
Sidney Gelman, Paterson, N. J.
Harry E. Gerner, Jersey City, N. J.
Ruth A. Guy, Boston, Mass.
Fred W. Jeffrey, Ottawa, Ontario, Can.
Marion G. Josephi, New York, N. Y.
Walter L. Mitchell, Jr., Newark, N. J.
Edward T. O'Donnell, Wilmington, Del.
Antonio Ortiz, Santurce, Puerto Rico.
Martin A. Quirk, Red Bank, N. J.
Samuel X. Radbill, Philadelphia, Pa.
Leo S. Radwin, Brooklyn, N. Y.
Joseph F. Raffetto, Asbury Park, N. J.
Ralph A. Ross, Brighton, Mass.
Milton J. E. Senn, New York, N. Y.
John F. Shaul, Bloomfield, N. J.
H. H. Shuman, Fitchbury, Mass.
Samuel Schwartz, Washington, D. C.
Benjamin M. Spock, New York, N. Y.
Morris Steiner, Brooklyn, N. Y.
James W. Stirling, Bellevue, Pa.
Nathan B. Talbot, Boston, Mass.
George M. Wheatley, Manhasset, L. I., N. Y.
Daniel A. Wilcox, Mount Kisco, N. Y.
Ernest M. Worden, Montreal, Quebec, Can.

Region II

Charles B. Alexander, San Antonio, Texas.
William J. Ball, Charleston, S. C.
Bessie Mae Beach, New Orleans, La.
Helen W. Bellhouse, Thomasville, Ga.
Lonita Boggs, Greenville, S. C.
Barnett P. Briggs, Little Rock, Ark.
Alice Drew Chenoweth, Louisville, Ky.
Herman W. Farber, Richmond, Va.
Kenneth B. Geddie, High Point, N. C.
Jack R. Hild, Houston, Texas.
George D. Johnson, Spartanburg, S. C.
Robert B. Lawson, Winston-Salem, N. C.
Robert C. McGahee, Augusta, Ga.
Masters H. Moore, Lawton, Okla.
Clifton T. Morris, Baton Rouge, La.
George R. Russell, Tulsa, Okla.
Mary Zeldes, Muskogee, Okla.

Region III

Russell J. Blattner, St. Louis, Mo.
Paul C. Crone, Cleveland, Ohio.
Lena S. Enright, Findlay, Ohio.
Robert C. Fredeen, Kansas City, Mo.
Walter Heymann, Cleveland, Ohio.
E. S. Lippman, Minneapolis, Minn.
George B. Logan, Rochester, Minn.
Thomas H. McEachern, Ann Arbor, Mich.
Robert J. McGillicuddy, East Lansing, Mich.
Mary Margaret McLeod, Petoskey, Mich.
Harry Medovy, Winnipeg, Manitoba, Can.
Robert Rosenthal, St. Paul, Minn.
Katherine Ver, Dayton, Ohio.
A. Alvin Wolf, Chicago, Ill.

Region IV

Edmund M. Cairns, Lethbridge, Alberta, Can.
Howard L. Eder, Santa Barbara, Calif.
Clinton Hollister, Santa Barbara, Calif.
Clarence L. Lyon, Spokane, Wash.

Dr. S. Josephine Baker, of Belle Mead, N. J., and Dr. Julius Levy, of Newark, N. J., were elected to Associate Fellowship upon the recommendation of Dr. Stanley Nichols.

Dr. Grulee read a letter from Mr. John Mosby of The C. V. Mosby Company regarding subscriptions to the JOURNAL for men in the armed services, offering the JOURNAL at the rate of five dollars a year. It was decided to give the men in service their choice as to whether or not they wished to subscribe for the JOURNAL. After further discussion, it was voted to accept The C. V. Mosby Company's offer if the letter meant only those who wished the JOURNAL, but if, upon further inquiry, the letter meant that the Academy would be charged for the subscriptions of all the men in service, the offer would not be accepted. Moved and carried.

Mr. Lawrence H. Selz, in person, gave his report on publicity.

Annual Meeting.—It was decided to hold the annual meeting, in spite of the present emergency, at the Palmer House, Chicago, Ill., November 4-7. Dr. Martmer presented an outline of the program, and further arrangements and decisions were left to the Program Committee, the Secretary, and the Local Committee.

The difficulties of having a Clinic Day this year due to discontinued bus service were discussed. It was suggested that a dinner be held with limited, dignified entertainment, which suggestion was voted on, moved, and carried. The matter of a registration fee, including the dinner ticket, was discussed, and it was decided to refund half the value of the ticket to those who were unable, or did not care, to attend the banquet, provided the ticket was forwarded to the Secretary's office after the meeting. This was accepted as the future policy of the Academy.

Discussion regarding the commercial exhibits followed. It was decided to follow the present policy of the Academy in that respect in accepting only those products for exhibition purposes which have been approved by the American Medical Association, provided they were subject to such approval.

It was agreed that Dr. Hugh McCulloch should be asked to continue his exhibit, since it was considered a decided asset to the meeting.

Committees.—The report of the Committee on Camps was read and accepted.

The report of the Committee on Contact Infection was read and accepted. The Executive Board agreed that full cooperation should be given the American Tuberculosis Association, and it was voted, moved, and carried that a definite program be prepared and followed.

The report of the Committee on Cooperation with Nonmedical Groups was read and accepted. It was recommended that this Committee investigate the status of health laws in relation to nursery schools and report to the Executive Board at the next meeting in November. In regard to this, it was felt that some definite action was very necessary leading to the passing of state laws for nursery schools much the same as those which now govern public schools, and that we, as an Academy, could make such recommendations.

The report of the Committee on the Fetus and Newborn was read, and it was moved, seconded, and carried that the Executive Board accede to the Committee's requests that Dr. Mitchell I. Rubin be added to the Committee; that they pass upon a code for the classification of the diseases and conditions found in still- and liveborn infants in the neonatal period and an outline for a complete autopsy report on the newborn infant; that they be given the right to sponsor a film on the "Care of the Newborn" to be prepared by Mead Johnson & Co.

Two letters from the Chairman of the Committee on Mental Health were read. The advisability of sending the scenario of the film, "Emotional Growth During Infancy," to all the members of the Academy was discussed. It was decided to send the scenario only to members of the Committee, the Executive Board, and those especially interested in this line of work, and that the latter group be solicited through an advertisement in the JOURNAL, asking that those who are interested to please send their names to the Secretary.

Regarding the paper entitled, "The Reaction of Children and Youth in Wartime," written by the Chairman of the Committee on Mental Health, Dr. Bert I. Beverly, it was agreed upon that the distribution of this paper, in reprint form or otherwise, should be left in the hands of Dr. Veeder and the Secretary.

The report of the Committee on Medical Education and Postgraduate Education was read and accepted.

The report of the Committee on Nursing Education, as well as the report of the Committee on Pan-American Scholarships,* were read and accepted.

The winners of the E. Mead Johnson Awards were announced, and it was decided to inform Mead Johnson & Co. that four certificates should be printed in reply to their inquiry.

The report of the Council for Pediatric Research was read and accepted.

Dr. Otto Goehle submitted a rather lengthy report of the Committee on Geographical Distribution of Pediatricians. It was the consensus of opinion that this report would be of value eventually and that Dr. Goehle should be informed that the Executive Board was interested in it and requested that different phases of it be prepared in abbreviated form for publication in THE JOURNAL OF PEDIATRICS. Dr. Grulee was authorized to furnish Dr. Goehle with a new directory or other supplies that he may need to finish this survey.

The report of the Committee on Mothers' Milk Bureaus was accepted and approved as read, as well as the reports of the Committee on National Defense and the Committee on Tumor Registry.

*A full report of this Committee appears on page 263.

Reports of Regional Chairmen

Region I.—Dr. Charles K. Johnson, of Burlington, Vt., was appointed State Chairman to replace Dr. Paul D. Clark, who has entered the armed services of the United States; Dr. Joseph A. Gilmartin, of Pittsburgh, was appointed Co-chairman of Pennsylvania to replace Dr. E. R. McCluskey, who is also entering the armed services.

Dr. Nichols presented a resolution from Region I regarding Child Health Responsibilities During the War. It was stated that directly there was little the Academy could do, but indirectly there was a great deal that should be done. Any suggestions along this line could be printed in the JOURNAL for the attention of all Academy members.

Dr. Nichols also presented a resolution in connection with the utilization of pediatricians in the war. The Executive Board felt that since Region IV and the Academy had presented a resolution very similar to this one to the powers that be last year, it would be best for Region I to send in this resolution in the name of the Region only.

Region II.—Dr. Hugh Leslie Moore reported that there would be a meeting of Region II in conjunction with the meeting of the Southern Medical Association for which an assessment would be made on the members of Region II, since they had no funds in their treasury.

Region III.—Dr. Arthur H. Parmelee, of Oak Park, Ill., was appointed State Chairman to replace Dr. James H. Wallace, who has entered the armed services, and Dr. Frank Van Schoick, of Jackson, Mich., was appointed State Chairman to replace Dr. Wyman C. C. Cole, also entering the armed services.

Dr. Lee Forrest Hill presented a resolution which had been unanimously passed at the meeting of Region III in Cleveland that "the American Academy of Pediatrics be open to all who are eligible for membership regardless of race, color, or creed." After discussion, the Secretary was authorized to state that every case which had come up for consideration had been considered by the Executive Board as individuals, and that there is nothing in the Constitution and By-Laws of the Academy which would exclude anyone because of race, color, or creed.

Dr. Lee Forrest Hill suggested that a moving picture on the subject of Nutrition be projected as a definite Academy effort. It was stated that Mead Johnson & Co. would be very glad to assist in this effort and that something along the line of slides and charts would perhaps suffice. It was moved, seconded, and carried that such a movie should be originated along the lines of Nutrition and the Nutrition Program, with Dr. Joseph S. Wall as Chairman of the Committee. Dr. W. H. Sebrell and Dr. Katherine Bain were also suggested for this Committee, and Dr. Wall could add any others whom he might wish. (In this connection, a representative from the American Legion demonstrated a slide sound machine to the Executive Board. It was felt that this machine definitely had its possibilities and should be considered in this Nutrition project.)

Region III presented the following resolution which was approved by the Executive Board. It was suggested that a copy of this be sent to each member of the Executive Board and State Chairman with the request that he send on this resolution to his Congressman with a personal letter. A list of names to whom this resolution should be sent was presented.

> WHEREAS, the war has led to the displacement of large groups of population and of unusual concentration in and around industrial areas and military camps, and in communities totally unprepared to meet the medical situation resulting; and
>
> WHEREAS, inadequate provision has been made to safeguard the health of and give adequate medical care to the thousands of children in these areas; and

WHEREAS, it is apparent from reports by our members from every state in which these developments have taken place that the situation is not only dangerous to the present health, but to the future welfare of these children; and

WHEREAS, adequate medical care is essential to the morale of industrial workers and to the men in service who have left their families; and

WHEREAS, it is apparent that adequate medical care for the children in these areas cannot be supplied through the efforts of the local medical profession alone

BE IT RESOLVED by the American Academy of Pediatrics:

1. That immediate attention be given to this situation by the proper governmental agencies concerned with the health and morale of our industrial workers and civilian population.

It recognizes:

a. that inasmuch as these areas are largely due to munition industries, it is the concern of the military departments.
b. as a matter of public health, it is the concern of the Public Health Service
c. as relating to the health of children, it is the concern of the Children's Bureau.

The Academy is not concerned through which agency, or combination of agencies, this service is furnished or administered, as this is a matter of executive arrangement and detail, but that the problem demands immediate attention.

2. That careful consideration be given to the proper placement to meet these needs of physicians adequately trained in child health and further that provision be made for the recognition of these services as being a part of our war effort.

Region IV.—Dr. Edward B. Shaw presented a program of Child Health Education which was carried out by the San Francisco members of the Academy with the idea that such a program be undertaken in other sections of the country.

An outline of the activities of the Academy during the War was presented by Dr. E. C. Mitchell and discussed before presentation to the American Legion.

The question of the advisability of furthering the project for a pediatric library and museum to be fostered by the American Academy of Pediatrics was discussed at some length. It was decided to appoint a special committee to look into this situation with Dr. Edgar E. Martmer as Chairman. The following members were appointed to this Committee: Dr. Ernest Caulfield, Dr. Albert D. Kaiser, and Dr. Hugh McCulloch.

With respect to the proposition of endorsing an institution for the investigation of child health and development, which Dr. William Palmer Lucas is sponsoring in San Francisco, it was decided that while the Executive Board most heartily approved of this effort, it did not feel that it could put itself in a position to endorse any such institution, since in the past it had refused like propositions on several occasions.

While the Executive Board very heartily approved of an honor roll for men in service, it was felt the best we could do now was to print the names as we gain knowledge of them, and only at the end of the war could a compiete honor roll be printed.

The Secretary was authorized to develop Latin-American fellowships among the pediatricians of the Central and South American regions.

Again the question of whether or not the Academy should have a key, or like insignia, for members was brought up by a member. It was decided to submit this matter to the members of the Academy by questionnaire, the result of which will be reported later.

The question of life membership was discussed and it was decided not to have such a membership in the Academy.

Dr. Edgar E. Martmer presented a very complete and detailed book of instructions which should govern both regional and national meetings. This is being mimeographed and will be used for the purpose intended.

Dr. Ernest Caulfield presented an outline of his work as historian of the Academy which was approved with much appreciation.

Report of the Committee on Pan-American Scholarships

Since the report of the Committee on Pan American Scholarships, published in the August, 1941, issue of THE JOURNAL OF PEDIATRICS, we have been able to contact pediatricians in Brazil, and in São Paulo the following committee has been formed:

Prof. J. E. Santos Abreu, President of the Section on Pediatrics of the São Paulo Association of Medicine

Prof. Pinheiro Cintra, Professor of Pediatrics

Prof. G. H. Paula Souza, Professor of Hygiene and Director of the Hygiene Institute of the São Paulo University

Prof. Pedro de Alcantara, Professor of Pediatrics

Dr. Octavio Ganzaga, Director of the Institute of Puericulture of the State Health Department

Dr. Jorge de Queiroz Moraes

Dr. Mario da Silva Margarido, Ex-President of the Section on Pediatrics of the São Paulo Association of Medicine, and Dean of the pediatricians of São Paulo

Since the pediatricians in Rio de Janeiro seem to form a very distinct group of their own, we have also endeavored to make contacts with this group, and Dr. Adamastor Barbosa, President of the Brazilian Society of Pediatrics in Rio de Janeiro, has written me that they are in the process of appointing a scholarship committee. It is hoped that eventually the Brazilian scholar will be selected by cooperation of both committees.

Dr. Paulo de Barros Franca has been selected as a candidate by the committee in São Paulo, but in view of the war conditions he felt it advisable to postpone his journey to the United States, and we are holding a place open for him for the time being.

Dr. Julio Meneghello from Chile and Dr. G. Cardelle Penichet from Cuba have almost completed their year of work at Harvard University, and so has Dr. Fernando Madero from Mexico, who spent a year at the University of Chicago. We have been informed that the Venezuelan scholar is planning to arrive here next September, and that Argentina, too, will be ready to send a young pediatrician in the near future.

Because of the war, it has not been possible this year to fill the regular scholarships, and therefore, we have felt it advisable to accept a scholar from Panama, Dr. Leopoldo Benedetti, who was the official delegate from Panama at the Eighth Pan-American Child Congress. He is beginning his work at the University of Cincinnati.

ELEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

BOSTON, MASS.—OCT. 10, 1941

Panel Discussion on Intestinal Obstruction in Infancy

Chairman: William E. Ladd, M.D., Professor of Child Surgery, Harvard Medical School; Chief of Surgical Service, The Children's Hospital, Boston, Mass.

Associates: Edward J. Donovan, M.D., Assistant Professor of Surgery, College of Physicians and Surgeons, Columbia University; Attending Surgeon, St. Luke's Hospital; Babies Hospital, New York City, N. Y.

Robert Edward Gross, M.D., Associate in Surgery, Harvard Medical School; Associate Visiting Surgeon, Children's Hospital, Boston, Mass.

CHAIRMAN LADD.—I am going to ask Dr. Donovan to answer the first question which has been presented.

QUESTION.—Is it normal for a newborn baby to vomit bile or should one suspect an intestinal obstruction under these circumstances?

DR. DONOVAN.—It is distinctly abnormal for a newborn baby to vomit bile, and one should suspect intestinal obstruction whenever this happens.

QUESTION.—What are most common forms of intestinal obstruction in infancy?

DR. GROSS.—We can answer this question best by reviewing a few of the statistics in the Surgical Service at the Children's Hospital in Boston.

During the last twenty years the most common type of intestinal obstruction has been that of pyloric stenosis, with a series of approximately 850 cases.

The next most common type has been that of intussusception, a condition which appears somewhat later in life, usually in the latter part of the first year. There is a total of 510 such cases.

Not exactly relating to the intestine, but having to do with the alimentary canal, are those obstructions about the anus and rectum. Of these, we have had 240 cases.

The next type is that which arises from incarcerated inguinal hernia. We have had 140 such cases, most of which occurred during the first eighteen months of life.

Another form is that usually found in neonatal life having to do with intrinsic malformation of the intestine itself, such as atresia or stenosis, of which we have had a series of about 80 cases.

An important type of obstruction is that due to malrotation or incomplete rotation of the intestinal tract, of which we have had a series of 50 cases.

An unusual obstruction, not exactly having to do with the intestine but yet a part of the alimentary canal, is atresia of the esophagus. We have had 35 such cases.

Next come duplications, which are relatively rare, which may occur at any level of the alimentary tube from tongue to anus. In this group we had 20 individuals.

Finally, there are those baffling forms of intestinal obstruction in newborn babies which are dependent upon a highly viscid and sticky meconium. We have had 15 cases of this type.

QUESTION.—How can you differentiate between the vomiting of central nervous system origin and that of gastrointestinal obstruction?

CHAIRMAN LADD.—This question is a good question but it is a very difficult one to answer.

The best way to answer it is to consider individually some of the types of intestinal obstruction, give their symptoms, and then point out the differences between the vomiting of central nervous system origin and that caused by gastrointestinal obstruction.

Dr. Gross has said that the most common condition is pyloric stenosis. I never have operated on an infant with a subdural hematoma with an erroneous diagnosis of pyloric stenosis, but it has been done.

Taking the symptoms of pyloric stenosis, you might put it this way: "How would you make a diagnosis of pyloric stenosis?"

In the first place, it is a condition more common in the male than in the female, in the proportion of 85 per cent to 15 per cent.

The next most prominent feature is vomiting. And the vomiting is quite characteristic. It usually starts about the tenth to the fourteenh day of life and becomes progressively worse. It may almost stop for two or three days, with only occasional vomiting, but then it progresses and eventually becomes a situation where almost all food is vomited. The vomiting has some other characteristics. It is explosive in character, and it usually comes comparatively soon after the ingestion of milk.

The next distinguishing feature is the visible peristalsis, which is seen in the epigastrium running from left to right and which is a most important sign of pyloric stenosis.

The next three symptoms or signs are the loss of weight, dehydration, and scanty stools, the latter often referred to as constipation. It is not constipation; it is lack of stools rather than the impaction of stools.

There is one more sign which is important and which is seen in practically every patient, and that is the palpable pyloric tumor.

If we have these five signs—explosive vomiting, visible peristalsis, dehydration, scanty stools, and a palpable pyloric tumor, one can be quite certain of the diagnosis of pyloric stenosis.

QUESTION.—How could you distinguish the symptoms and signs of a central nervous system lesion from those of pyloric stenosis?

CHAIRMAN LADD.—The vomiting of central nervous system origin, though perhaps explosive in character, does not necessarily have any relation to feeding. It might come on after feeding or it might appear at any time. The vomiting is not so apt to be constant or progressive; in other words, it might be present for a few days and then disappear for a period. In contrast, the vomiting of pyloric stenosis is more apt to come on after the intake of food and to become more severe and more frequent as the baby grows older.

With a central nervous system lesion the fontanel is often tense or bulging. Furthermore, the eyes may have a peculiar look; they are prone to have a stary and abnormal appearance which is rather difficult to describe. There may or may not be convulsions.

The next question is the change in reflexes. Alterations in reflexes may be absent or minimal. The skull of a baby is very adaptable and pliable, and it is the exception rather than the rule to find any localized neurologic signs, even if you have a localized lesion.

Finally, the eye grounds are abnormal in about two-thirds of all babies who have central nervous system disease.

In summary, there are many points which help to differentiate the clinical picture of pyloric stenosis from that of central nervous system disease. The mistake should not be made very often.

QUESTION.—If intestinal obstruction is being considered as a possible diagnosis for a patient, when is it permissible or advisable to administer a purgative?

DR. DONOVAN.—It is never advisable or permissible to administer a purgative while intestinal obstruction is being considered as a possible diagnosis.

Purgatives set up a very violent peristalsis, and you may convert an incomplete obstruction into a complete obstruction or you may cause perforation of the intestine by setting up such vigorous activity of the intestine or colon. The same is true concerning the use of pitressin. A great deal of trouble may be caused by using a purgative, or pitressin, or any of the drugs that increase peristalsis.

QUESTION.—Is there any contraindication to giving an enema if intestinal obstruction is suspected?

DR. DONOVAN.—There is no contraindication if the enema is carefully given. An enema can do little harm if gently administered. It must be given without using too much force.

CHAIRMAN LADD.—Anyone who has seen the action of pitressin experimentally on animals and who has seen the extreme vigor of the intestinal peristalsis as the result of the administration of this drug can realize how much harm it might do in the patient with intestinal obstruction.

QUESTION.—How can you differentiate the obstruction of pyloric stenosis from pylorospasm or other forms of intestinal obstruction?

DR. GROSS.—Let me answer the last part of this question first. The age of the patient is of some importance, because those individuals with pyloric obstruction, whether it be pyloric stenosis or pylorospasm, are usually in a definite age group, between 10 days and about 2 months, whereas other forms of intestinal obstruction occur at different periods. Intussusception, for instance, is most apt to appear during the latter part of the first year, whereas symptoms from intestinal atresia or intestinal malrotation are apt to come on shortly after birth, most frequently in the first week or ten days of life.

Another way in which pyloric obstructions can be differentiated from obstruction of the small intestine is by the general appearance of the abdomen. If pyloric obstruction is present, the distension is limited to the upper abdomen, whereas obstruction of the lower intestinal tract is apt to give rise to a generalized abdominal distension.

The next way in which differentiation is made refers to the visible intestinal patterning. In pyloric stenosis, the waves can be seen passing from left to the right side of the epigastrium; whereas in obstruction of the small intestine the pattern is more widespread and the waves can pass in any direction.

Whenever obstruction of the small intestine is suspected, a stethescope should be placed on the abdomen. When obstruction exists there are definite peristaltic rushes, so that one can usually hear the increased peristaltic activity.

Finally, if there is any question about differentiating pyloric from intestinal obstruction, roentgenologic examination should be resorted to. This is not always necessary, but when called upon it will almost certainly settle the issue at once.

Now, to answer the first part of the question concerning the differentiation of pyloric stenosis from pylorospasm. First of all, with pyloric stenosis the symptoms are usually progressive. When the child once begins to have trouble, he generally has increasing difficulty as the days go on; he vomits more and the symptoms

become worse. In contrast, with pylorospasm there is apt to be a periodicity of symptoms; they are worse for a few days and then they appear to be better and subsequently get worse again.

Second, the baby with pylorospasm is more apt to be one who is spastic. I do not mean to infer that the child has a definite nervous system damage, but he has an increased muscular tone, and is more apt to be fussy and irritable.

The third way in which we differentiate the obstruction of pyloric stenosis from pylorospasm is by feeling of the tumor. The tumor can be felt in pyloric stenosis, whereas no mass is felt in the case of pylorospasm. In pyloric stenosis one should be able to feel the tumor in about all cases, provided the examiner is patient and takes time to palpate the abdomen properly.

Finally, these two conditions might be differentiated in some cases by the reaction to drugs, because the individual with pyloric stenosis is usually not relieved when sedatives or antispasmodics in the form of phenobarbital or atropine are given, whereas the individual with pylorospasm usually gets prompt relief from the use of these drugs. In most cases pylorospasm can be satisfactorily differentiated from the pyloric stenosis, but if any question arises, a few days' trial with phenobarbital or atropine will usually make clear which of these two conditions exists.

QUESTION.—What factors are important in attaining a low mortality in treatment of congenital hypertrophic pyloric stenosis?

DR. DONOVAN.—The factors that are important in attaining a low mortality in treatment of congenital hypertrophic pyloric stenosis are, first, early diagnosis. Dr. Gross has presented that very nicely. The diagnosis must be made early, if babies are to be operated upon while they are still good surgical risks. The history is certainly important and runs pretty true to form in most of the cases. We must differentiate, as Dr. Gross points out, the pylorospasm from pyloric stenosis. The clinical pictures may be quite similar, the main difference being that one has a palpable pyloric tumor and the other has not.

We are finding, certainly in our part of the country, that the diagnosis is being made very much earlier than it was two or three years ago, and we feel very much encouraged about this state of affairs. These babies are coming into the hospital in very much better condition than they were a few years ago.

When the diagnosis has been made, another important factor is the isolation of the babies, particularly if they are not in good condition. If their resistance to infection is very low, we place them in a room we have set aside, called the pyloric room, where no patients except pyloric babies are kept. Visitors are not allowed in this room. Even parents are excluded. Doctors and nurses wear masks over the nose and mouth when entering.

One of the most important things after diagnosis has been made is restoring the lost fluids. That is one factor that has brought the mortality rate down to the present low level. These babies must not be operated upon until their fluid balance has been restored to normal. I can remember very well that before this factor was emphasized lots of the babies died from what was called shock, which meant that they were not in condition to stand this perfectly simple operation. The mortality rate from shock at one time was as high as 15 per cent. This is so important that if necessary, take four or five or six days to prepare these children for operation. When body fluids are restored they can be operated upon and stand the procedure perfectly well. In restoration of lost fluids, physiologic saline will help to replace the depleted chlorides. When fluids and electrolytes have reached an optimum value, operation should be undertaken promptly.

The operation which is done almost entirely is the Fredet-Rammstedt. It is extremely successful and gives a permanent result, as has been shown by patients who were operated upon as long ago as 25 years and have had no further trouble.

One must perform a careful operation. The Fredet-Rammstedt procedure is a very simple one, but it is important to avoid cutting into the duodenum. I say that because I have done over 350 of these operations before that happened to me, and it has now happened twice. That does not mean that I have become careless; it is an accident which even the most experienced operator can have. The reason for the complication is that you pass from the very thick pyloric muscle into the duodenal musculature which is very thin; and at this point of transition the duodenal mucosa can be easily opened. When this happens, it is important to recognize it. If you see a little mucus or a little air come out of the incision it should indicate at once that the incision has been carried too far and that the duodenum has been punctured.

After operation the babies should be isolated in the pyloric room again, because of their low resistance to infection, and their fluid balance should be watched very carefully.

We routinely give them a hypodermoclysis once or twice a day, depending upon their condition, for the first three days after operation.

The postoperative feedings are very important. We find that these babies will take evaporated milk formula and tolerate it very well after operation.

Those, I think, are the most important factors in attaining a low mortality in hypertrophic pyloric stenosis.

CHAIRMAN LADD.—The next two or three questions I will ask Dr. Donovan to answer.

QUESTION.—Tell us something about the cases in which some vomiting continues after operation for pyloric stenosis.

DR. DONOVAN.—Quite a number of the babies vomit after they have been operated upon. The reason is that the stomach has not been completely emptied at the time of operation.

The last thing we do before making the abdominal incision is pass a stomach tube and completely empty the stomach. The baby has not had a feeding for three hours before operation, so what you are apt to get is a good deal of gas and some mucus, and it is surprising how much you will obtain.

There are two reasons for emptying the stomach. The stomach is very much easier to handle at the time of the operation if it is empty, whereas if you bring it out full of air the chances of cutting into the duodenum are very much greater. If the stomach is completely empty when the baby is sent from the operating room, he will not vomit. Postoperative vomiting is due in the great majority of cases to the fact that the stomach is not empty when the baby is sent back to the ward. If the baby vomits postoperatively, we pass the stomach tube immediately to empty the stomach.

Another factor is that a complete operation must be performed. It is not necessary to cut every single fiber of the circular muscles but it is necessary to cut most of them. You must not leave any sort of constriction. I would say if a complete operation has been done and the baby's stomach is empty when he is returned to the ward, he should not vomit after operation.

QUESTION.—How frequently have you seen an incomplete or inadequate Fredet-Rammstedt operation performed? If such a situation presumably existed, how long would you defer reoperation?

DR. DONOVAN.—I cannot quote any statistics but it happens fairly frequently. I do not know why it should happen but perhaps it is because the surgeons who are operating are conscious that they have to be very careful not to cut too deeply so they leave a little ring of tissue that should have been cut. If such a situation exists I would certainly proceed as I stated in answer to the last question. I

would wash out the baby's stomach and see if that did not help the situation. If it did not help I would not wait very long before operating again. If the baby was vomiting as he did before operation and had been given a formula that should be tolerated, I would not let that baby go more than four or five or six days without being firmly convinced that his operation was inadequate.

QUESTION.—What would be your criteria for the necessity of reoperation?

DR. DONOVAN.—There would be persisting vomiting after you had washed out the baby's stomach and had done all the tricks you knew about and the baby continued to vomit.

There might be added what would be done at the reoperation. There are two things I would do. One would be to try to fix up the first operation; that is, look at the duodenal surface to see if there was a ring of fibers there. If there was, I would cut it. I would try to make the incomplete operation complete. If that does not seem to be sufficient, it is possible to make another cut in the pylorus and do a perfectly new Fredet-Rammstedt operation.

QUESTION.—Do you give a blood transfusion routinely immediately following the Fredet-Rammstedt operation for pyloric stenosis?

DR. DONOVAN.—We almost never give a transfusion. There was a time we transfused routinely, and a great many of the babies who did not need it received blood transfusions. Then we went along for quite a while and picked out certain babies who we thought needed blood transfusions. Now we have come to the point where we never give a blood transfusion. You can restore body fluids perfectly well in a matter of three or four or five days without the use of a blood transfusion. You can do it perfectly well with saline or saline and glucose, so that it is not necessary to give blood transfusions and we do not do it at all.

CHAIRMAN LADD.—The question of pyloric stenosis seems to stimulate a good deal of interest.

QUESTION.—Have you observed with pyloric stenosis a coexisting obstruction of small bowel? What would be the surgical procedure in this double obstruction?

DR. GROSS.—Several times we have encountered obstruction of the small intestine in conjunction with pyloric stenosis. It usually means that one is driven to an operative procedure of considerable magnitude, and yet one which must be faced if the individual is to be saved. Our attitude has been to make a generous incision, which takes a relatively few minutes, perform the pyloromyotomy, and then proceed with the treatment of the small bowel stenosis. Our treatment for this has been a short-circuiting type of operation, depending upon the level of the obstruction, bringing the two loops together to relieve the obstruction by short circuiting the stenosis.

Summing up the answer to the question, a double lesion would require treatment of both of them at the same operative procedure.

QUESTION.—Differentiate between duodenal obstruction and pyloric stenosis.

DR. GROSS.—There are several ways in which this may be done.

The age of the patient is usually important because with the intrinsic duodenal obstruction these children usually begin to have symptoms within the first two days of life. In contrast, when pyloric stenosis is present, vomiting does not usually begin prior to the tenth day of life. Some infants with malrotations start to have trouble in the first few days, while others may get by for months or years before the lesion begins to give symptoms. In general, most of the infants with duodenal obstructions begin to give symptoms within the first two days or the first week of life, whereas pyloric stenosis makes itself evident a little later on.

In practically all duodenal obstructions there is vomiting of bile, while bile is characteristically absent from the vomitus of a pyloric stenosis patient.

If the site of obstruction is not entirely clear, x-ray examination will give conclusive evidence to settle the point.

QUESTION.—Is there any relation between pyloric obstruction and jaundice, due either to anomalies of the bile ducts or to other cause?

DR. GROSS.—I do not believe there is any relationship between the two, other than a coincidental one.

In a long series of cases of pyloric obstruction that we have had, and I am sure that Dr. Donovan will say the same thing, jaundice is extremely rare. There were a few instances of jaundice of the newborn infant. As far as I know there is no direct relationship between pyloric obstruction and obstructive jaundice. The one who wrote this last question added a note: I have in mind a 6-week-old infant who had persistent mild jaundice and developed projectile vomiting at about 5 weeks of age. Peristalsis was visible but not marked; no tumor felt; stools yellow.

This is insufficient data for me to hazard a diagnosis. I have seen an occasional baby with malrotation or a twisting of the mesentery of the intestines who had concurrent compression and obstruction of the common bile duct. It is barely possible that the case in hand has such an abnormality.

CHAIRMAN LADD.—We seem to be getting into a panel discussion on pyloric stenosis.

QUESTION.—If the patient is severely dehydrated and the case is a grave one, should operation be delayed until there is full restoration of fluids?

DR. DONOVAN.—Absolutely. There is no hurry about operation. It is all-important to wait as long as a week if necessary. It is surprising how well you can restore the body fluids in three or four days.

These babies never should be operated upon until their tissue fluids have been brought to normal. You will know by looking at the child when this state has been attained. He is a different looking baby than he was a few days before.

In short, operation should always be deferred until the patient is adequately prepared.

QUESTION.—How soon should the patient be fed after a pyloromyotomy?

DR. DONOVAN.—Two hours after operation he can be given 15 c.c. of water by mouth, and three hours after operation he can be started on his first feeding, which consists of 4 c.c. of evaporated milk formula and 4 c.c. of barley water. That is increased so that at the end of twenty-four hours he is receiving an ounce at each feeding.

Previous to two or three years ago we felt it was necessary to give all these babies breast milk. Breast milk has been rather expensive so that we have recently given up the idea of giving them breast milk and have employed a formula satisfactorily.

QUESTION.—How do you feel about the use of barium as an aid to the diagnosis of pyloric obstruction?

DR. DONOVAN.—I have a sort of obsession on that point. I feel that barium is not necessary or useful at all. It gives the baby a great deal of trouble after operation unless it is gotten rid of. It is never necessary to give barium to these babies.

Get the conditions right. Have the baby relaxed. The stomach should be empty. Then, when you examine the baby you can palpate the tumor in every single case and

I feel definitely that barium is contraindicated with all of these patients. It gives them a lot of postoperative discomfort and does not necessarily aid in the diagnosis.

QUESTION.—Do you feel that withholding fluid by mouth for twenty-four hours, postoperatively, gives a smoother recovery? This, of course, presupposes the use of parenteral fluid.

DR. DONOVAN.—It is not necessary to withhold fluid by mouth for twenty-four hours. The baby is starving; he is hungry, and fluid keeps him happy and quiet. It is beneficial to start feedings as quickly as you can after operation. It does not disturb the child the least bit to get fluids after operation.

CHAIRMAN LADD.—There are two more questions on pyloric stenosis.

QUESTION.—What is the proper method of repair when the duodenum is nicked at the junction of the pyloric and the duodenal mucosa?

CHAIRMAN LADD.—The simpler the procedure, the better. Everybody I know has nicked the duodenal mucosa once or twice. All we do is to take one or two fine silk stitches and close over the neck. We have never had a death following it.

QUESTION.—How often do you see adhesions to the pylorus following operation?

CHAIRMAN LADD.—We have had about 850 cases treated surgically, and I do not recall but one in which there were adhesions following the operation.

DR. DONOVAN.—We had just one. A vessel had been tied off with a silk stitch and that knot became adherent to the under surface of the liver. We no longer use anything to tie off these vessels, but it had been done in this particular case. All that was necessary to do at the second operation was to free the knot from the under surface of the liver and the obstruction was overcome.

CHAIRMAN LADD.—We have several questions on intussusception, so we will take up that subject next. I will read through all these questions and perhaps we can answer them all at once.

What methods do you use for the treatment of intussusception?

Is the attempted reduction of intussusception by means of barium enema ever justified?

In what percentage of cases of intussusception is the reduction of the invagination successfully accomplished by manipulation under the fluoroscope without operation?

Is it a safe procedure to reduce an intussusception by hydrostatic pressure?

How soon after intussusception can one expect to find blood in the feces by rectal examination?

Discuss the present status of the controversy as to hydrostatic reduction versus immediate surgical interference.

These constitute quite a series of questions. I think they are all important, and I have rather strong opinions about them.

At the risk of having some of you think I am getting senile, I will recall that at the time I first joined the staff of the Children's Hospital there had been only two cases of intussusception successfully operated on in the city of Boston, one by Dr. Arthur Cabot at the Massachusetts General Hospital, and one by Dr. John Munro at the Carney Hospital. Those were the only two cases that had been reported as successfully treated.

At that time the usual and customary treatment for intussusception was carried out by the general practitioner. Pediatrics was somewhat in its infancy, and the main emphasis in pediatrics was placed on percentage feeding and a few other

matters of that sort, which really occupied a good deal of the time and thought of the pediatrician.

We had a good deal of trouble in trying to persuade either the general practitioner or the pediatrician that intussusception was a surgical condition. I recall very well having seen the autopsy of a patient who had been enthusiastically treated by a general practitioner. The general practitioner had been convinced that the intussusception must be reduced by hydrostatic pressure, and he had taken a douche bag and inserted a rectal tube into the child's rectum. The intussusception did not seem to reduce when he had six or eight feet of pressure on it, so he added tubing and took the bag up one story. Even this did not seem to reduce the intussusception, so he took the bag up two stories and produced hydrostatic pressure equal to a column of water twenty-four or twenty-five feet high on the poor infant's rectum. The child died of shock and peritonitis!

We have made considerable progress since then, and most medical men now agree that intussusception is probably one of the most important surgical emergencies of childhood.

When we started with this work many years ago our mortality was very high. It was about 70 per cent. With a rate of 70 per cent or over I think the pediatrician and the general practitioner were a little justified in not being too anxious to turn cases over to the surgeon.

However, from that time, 1910 to 1912 up to the present day, our mortality has consistently dropped. Several years ago it came down to about 14 per cent, where it remained for two or three years. In 1939 the mortality was zero and in 1940 there was but one death.

If you analyze this series of something over 500 cases which we have had at the Children's Hospital, some rather striking findings appear. In the first place, it is evident that intussusception is most common around the sixth or seventh month of life.

The next striking thing is the type of infant in which intussusception occurs. It almost always appears in wonderful looking babies who are very well nourished and even fat—extremely healthy looking subjects. It comes almost always out of a clear sky, and a baby who is perfectly well one minute is screaming with pain the next. I think it is important for everybody to realize the importance of diagnosing intussusception. If you have a very healthy looking baby in the sixth or seventh month of life who is suddenly taken with severe colicky pains which last ten or fifteen minutes or more and who then has a period in which he has no pain and will sit up and play with his toys, that is the characteristic picture of beginning intussusception. To my mind, this characteristic picture in the early stages is one of the causes for an unduly high mortality in intussusception. If the general practitioner or the pediatrician is called to see a baby and happens to make his first visit during a period of remission from pain, he looks at this extremely healthy, fat, splendid looking baby who is sitting up playing with his toes or his toys, and he says, "Here is a neurasthenic mother who is just upset. There is nothing the matter with the baby." Years ago he was prone to prescribe a mild cathartic and tell the mother the baby would be well the next day. That is the worst thing he could do! He should be suspicious at once when he sees this type of baby with what the mother describes as an acute, very severe pain. He should pay attention to the mother's story. I think that is the most important factor in making an early diagnosis and in reducing the mortality.

Usually after two or three episodes of pain, the baby is prone to vomit. The vomitus at first is simply the stomach content. It is quite common for these babies in the first few hours after that to have a normal stool, and that also misleads the practitioner who has read in the books that the signs of intussusception are palpable

tumor, abdominal distention, and bloody stools. Those are all signs of intussusception, but they are all signs of intussusception when you have made a late diagnosis. The first signs are extreme pain of an intermittent character followed by vomiting.

QUESTION.—How much does rectal examination contribute to the diagnosis?

CHAIRMAN LADD.—A rectal examination always should be performed. We used to consider it a good deal like feeling the tumor in pyloric stenosis, because we used to see those cases late, and by rectal examination you could frequently feel the advancing point. If the advancing point has progressed so far that you can feel it by rectal examination, it is almost exactly like a normal cervix in a female vagina.

CHAIRMAN LADD.—The next question is pertinent at this point.

QUESTION.—When do you expect blood?

CHAIRMAN LADD.—That is variable. Sometimes we see blood in the stools within four or five hours of the onset of the attack, while in other cases it does not appear until ten or twelve hours have passed. It is a little more common to see it prior to twelve hours.

Various other questions regarding intussusception have been sent to me here and I can see from their general tone that a number of you are interested in the reduction of intussusceptions by rectal injection of air or fluid. If it will not bore you too much, I am going to review the history of how this form of therapy gained some popularity.

If you will go back to the turn of the century you will find Dr. Clubby, of Sydney, Australia, writing most excellent monographs on intussusception. He published, I think, several different papers on the subject, and each one reported a lowering mortality rate. In other words, his experience was very much like ours here and he attributed a large part of his falling mortality to what one might term "propaganda" among the general practitioners in his locality. He clearly emphasized that the better results were not so much dependent on the surgeon as they were on the medical men who made diagnoses promptly. It was very analogous to the situation we have found here.

Strangely enough, Dr. Clubby had an assistant named Hipsley. Dr. Clubby thoroughly tried reduction of intussusceptions by rectal injections of water. He first tried it as a means of reducing the intussusception, as a curative measure. He abandoned that and came to the conclusion that it was unsafe. He then used it as a preliminary step to surgery. He did it before operation and then operated upon every case. He then abandoned it entirely and said it was not only unnecessary but inadvisable and added to the shock sustained by the patient. He felt that it did not facilitate the operation enough to make it worth while.

I think Dr. Hipsley is responsible for a good deal of the interest in going back twenty-five or thirty years and starting enema treatment of intussusception over again. Dr. Hipsley worked with Dr. Clubby and saw some cases reduced. Then he became enthusiastic about it and, with the more common use of barium and x-ray visualization, arrived at the conclusion, and correctly so, that he could reduce a certain number of these cases. Then he published one or two papers in which he gave a very low mortality, and if you read his papers through hurriedly you get the impression that this is a very desirable treatment. But if you read the papers carefully you will come to the conclusion that it is not so desirable after all, because Hipsley reports a 5 per cent mortality, if I remember his figures rightly, in the treatment of intussusception by enemas in patients who are seen within the first twelve or twenty-four hours. Their mortality rate looks favorable, but our mortality is zero for patients we see in the first twenty-four hours. So I do not think he has anything on us in the early cases.

There is another group in London who have become enthusiastic about this form of treatment, but if you will analyze the statistics in relation to durations of patients' symptoms, you will find the results are good with the very early cases (but they are not as good as the operative treatment) and that in the late cases they are not nearly as good. In summary, a 5 per cent mortality with treatment by hydrostatic reduction looks good, but if you study the facts carefully, the method does not give as good results as surgery does.

My prime objection to the attempt at reducing these by enemas is that I think it is not sound. We have tried it. We have had some x-ray men who have been enthusiastic about it. We have had other x-ray men who were sold on the idea and who said that they could tell when an intussusception was reduced. But I just do not think they can. On some occasions I have been told that an intussusception was completely reduced by a barium enema under fluoroscopic observation and control. In spite of this report I have proceeded with operation and have found anywhere from six to eight inches of gut still invaginated! It is usually imposible for the roentgenologist to visualize what is happening above the ileocecal valve. Any one who employs the enema treatment of intussusception is bound to get into trouble sooner or later and is bound to produce a high mortality in his community.

Let me go back again and say that I think really it is up to you men to keep down the mortality of intussusception. The way to keep it down is to make the diagnosis on the first visit and get the best surgeon you know to perform the operation immediately.

CHAIRMAN LADD.—There are several other questions that have come in on intussusception which are important, but we cannot be quite so dogmatic about the answers.

QUESTION.—What do you do when you cannot reduce an intussusception by operation?

CHAIRMAN LADD.—From the outset it is clear that if diagnoses are made early enough, there will not be many irreducible intussusceptions. A late diagnosis is not always the fault of the medical man; it is sometimes the neglect of the parents, who do not want to summon a doctor and who wait until the child has gotten into extremis before they call on him. We do not see so many irreducible cases as we used to, though we still see them too frequently.

When you cannot reduce an intussusception, there are three procedures which have been recommended. The first one should be thrown into the discard at once. This consists of leaving the intussusception mass in the abdomen and doing an enterostomy above it. There is nothing to justify such a procedure. It leaves a dirty gangrenous mass inside the abdomen, which gives rise to a high toxicity. This form of therapy should be completely abandoned.

The other two methods of treatment are resection with an anastomosis, and resection with a double-barreled enterostomy. Though our results are pretty nearly even with these two methods, we have come to the conclusion that of the two methods we lean toward resection of the intussusception mass and establishment of a double enterostomy (with later clamping the spur and closing the enterostomy). As years go by I think we will find that our results are far better with such an operation than with the immediate anastomosis.

There is one thing which almost every textbook on surgery mentions, and which I am sure is wrong. It is stated that intussusceptions are irreducible because of adhesions between the intussusceptum and the intussuscipiens. It is seldom true. In 500 cases we have seen only two or three examples of such adhesions. Difficulty in reduction is caused by the swelling of the mesentery and the edema of the intussusception mass.

I want to make one or two comments on the treatment of intussusception which I believe are important. In the early cases that are reduced easily, one does not have very much trouble with the postoperative care. The child goes along very smoothly, it is well in a week or ten days, and is ready for discharge soon after that.

In contrast, the late case is apt to have a great deal of trouble after operation, particularly in the form of a high temperature. It is quite common to have an extremely high fever for twenty-four to forty-eight hours after the operation. There has been a great deal of experimental work done to find out just what is the cause of this fever, but the exact mechanism is not yet clear. Obviously it is not bacterial infection because it appears so promptly and disappears so quickly. The best way we can combat it at the moment is to administer liberal amounts of parenteral fluids. Presumably the reason this administration of fluids is successful is that the "toxins" are diluted and carried off by the urinary tract.

While we are talking about intussusception, we should mention the subacute form which is rather a rare bird and which is more difficult to diagnose than the acute intussusception. The acute intussusception, if not relieved in forty-eight hours, soon becomes fatal. Every now and again we see a case in which the obstruction is not complete. There is usually some pain and some vomiting. It occurs more commonly in cases with a very long mesentery, and the circulation of the bowel is not cut off; and one does not get as much edema as in the acute case, which causes complete obstruction. Sometimes these subacute forms are quite easy to reduce even though they have been present a long time.

QUESTION.—What about the mortality rate if operated on after the second day?

CHAIRMAN LADD.—The mortality rate, as I stated before, in the first twenty-four hours is nil. It goes up rapidly after thirty-six hours, and when you get to forty-eight hours, the mortality is very high.

QUESTION.—What percentage of cases recur?

CHAIRMAN LADD.—We have had a number of recurrences, perhaps eight or ten, and a fair proportion of these recurrences took place in patients who had been operated on elsewhere and in whom operative procedures had been done to prevent recurrence.

We have had no mortality in patients who have had a recurrence. This is so because a recurrence gives symptoms which are immediately appreciated and recognized by the mother, who immediately brings the child to the hospital or physician without delay. So we get patients with recurrences earlier than any other patients. They are practically always brought in very promptly and, as I say, we have had no mortality in the cases of recurrence.

To sum up, I would say we do not do any operative procedure to prevent recurrence for three reasons: (1) they are not very successful; (2) they may prolong the operation just enough to turn a successful result into a fatal one; (3) the mother practically always notices the recurrence promptly and brings the child in before he has become dangerously ill.

QUESTION.—Is there any relationship between the onset of intussusception symptoms and feeding? In other words: Is it found most often on a full or an empty stomach; what time of the day does intussusception usually begin?

CHAIRMAN LADD.—My impression is that intussusception begins at any time of the day or night.

QUESTION.—Is abdominal distension necessarily a part of the clinical picture of intestinal obstruction?

DR. DONOVAN.—In low obstruction you almost always have abdominal distension. In high obstruction you never have. We have seen cases where people have remarked about the fact that there was no visible peristalsis and no abdominal distension. It is extremely important to remember that in high intestinal obstruction you may have no visible peristalsis and you may have no abdominal distension. In a low obstruction you may have both of these, and they may come on suddenly. In high obstruction the thing to remember is that you can have complete obstruction without visible peristalsis or abdominal distension.

QUESTION.—If a diagnosis of intestinal obstruction has been made, what measures should be taken to prepare the baby for operation?

DR. GROSS.—One of the most important things in preparing for operation on a baby who has intestinal obstruction is to place a catheter through the mouth or nose down into the stomach to aspirate the gastric contents. A child who is continually vomiting because of intestinal obstruction can easily aspirate this material and die of suffocation or pneumonia. One of the most important measures in treating any infant with obstruction is to clean out the stomach. It can be easily done with a soft rubber No. 8 or No. 10 urethral catheter.

The second thing which should be done for these babies is to restore their fluid balance. This should be started immediately. It has been our routine to inject 10 per cent glucose solution into a vein—usually 10 c.c. per pound of body weight. Then we give them physiologic saline in a clysis, 15 c.c. per pound of body weight.

Blood is not given to all infants, but is employed if there is any appreciable degree of shock or circulatory collapse. If there has been a great loss of blood, such as is the case with advanced intussusception, any important anemia should be combated by transfusion prior to operation. It is not always necessary, but in some infants it may be a life-saving measure.

In the very young, that is, within the first ten days of life, a small transfusion may be of importance to combat any existing bleeding tendency. We feel that all children who are operated upon within the first ten or twelve days of life should have a small transfusion or else one of the vitamin K preparations.

A reasonably complete physical examination should always be made. This is particularly true of infants with congenital obstruction of the intestine, because there may be other malformations which are just as important as the obstruction itself. There may be pulmonary atelectasis. All too often additional anomalies have been found after operation which should have been detected before.

As far as drugs are concerned, a good deal depends upon the type of anesthesia which is to be employed. We use ether on practically all of these patients and hence give atropine in adequate doses to dry up the oral and bronchial secretions, to insure a more even anesthesia. In babies under 1 month of age we do not use morphine because it has too depressing an effect on the respiratory center during anesthesia. In older children it is well to give morphine preoperatively. A third drug, coramine, should be considered. I have seen infants, within the first day or two of life, who have had considerable difficulty with respiration during general anesthesia. They have seemed to be improved by the stimulation which coramine gives to the respiratory center.

As far as the choice of anesthesia is concerned, a great deal depends upon the capabilities of the available anesthetist. In general, open mask drop ether is probably the safest anesthetic. We are fortunate in having anesthetists who do nothing else but work with babies and children. In most other communities the surgeons are not so fortunate in that respect as we are. If a good anesthetist who has had experience with children is not available, one might be better off with local novocain anesthesia. In general, we have advised against novocain in these small patients because they may develop subsequent trouble with wound healing, if novocain is extensively used.

QUESTIONS.—What should be the course of treatment of congenital duodenal obstruction?

Is it ever advisable to administer barium by mouth for contrast media in obtaining roentgenograms of gastrointestinal obstruction?

DR. DONOVAN.—Congenital duodenal obstructions may be divided into the intrinsic form, which means that the lesion is inside the lumen of the duodenum, and into the extrinsic type. The intrinsic duodenal obstructions may be from a membrane or diaphragm. If this completely occludes the lumen, it is called an atresia; if it incompletely occludes the lumen there is a stenosis. The two are varying degrees of the same thing. In contrast, the extrinsic causes are developmental bands, volvulus, and fixation of the duodenum in abnormal position so that some external structure presses against it.

In the course of treatment of congenital duodenal obstruction, it is important to make the diagnosis as quickly as you can. It should always be kept in mind when a baby has been vomiting bile. Then you attempt to determine whether the obstruction is complete or incomplete. The lesions which give a complete obstruction make themselves apparent in the first few days of life. The extrinsic lesions, on the other hand, may give symptoms in the first few days after birth or they may not show up until many months later.

The diagnosis should be made early, and here we can incorporate the second question.

From sad experience I would say that it is not advisable to administer barium by mouth in cases of suspected intestinal obstruction. We have done it in a patient with volvulus. The intestinal tract at the point of the volvulus was perforated and the barium was all over the peritoneal cavity when the baby was operated upon and, of course, he died. I feel definitely that you can usually get as much information from a plain plate of the abdomen in a high obstruction as you can by giving barium.

It is nice for the surgeon to have some idea before he starts to operate, as to just exactly where the obstruction is, and it is nice to have x-rays, but I think it is really dangerous to use barium, and I feel it should not be done.

After a diagnosis has been made, treatment should be started by restoration of lost fluids. Indeed, this can be commenced before the diagnosis is finally arrived at. The diagnosis having been made, the next thing is operation, in spite of the fact that it may mean that a newborn baby has to withstand an extensive operation. If there is an intrinsic obstruction (either stenosis or atresia), a duodenojejunostomy is made in front of or behind the colon. If there is extrinsic duodenal obstruction because of a volvulus, the intestinal mass must be untwisted. If there is extrinsic duodenal obstruction from a band, this must be divided. In short, all duodenal obstructions can be effectively treated if the operator promptly recognizes the type of pathology present and quickly institutes these accepted measures of relieving the obstruction.

QUESTION.—What surgical procedure is advisable and what results can be expected in cases of congenital tracheo-esophageal fistula?

CHAIRMAN LADD.—This question has been a very interesting one to me, and I have been prognosticating for a good many years that we were going to get some of these patients well some day.

They are very difficult cases to handle, and until recently the mortality has been 100 per cent. We have come terribly close to getting two or three of these patients well and we have one now who is living. I am not sure whether you will call him well, but he has been living for more than a year following operation.

I think it would be well to tell you of what our experience has been. In the first place, we have to go back to the embryology. You will find that these malformations are really quite uniform in character. They might be divided into four types.

We have the first type in which both ends of the esophagus end blindly and neither end communicates with the trachea. That is the easiest type upon which to operate and the one that offers the best hope of success. Unfortunately it is the rarest.

The next type is the one with the upper end of the esophagus entering the trachea and the lower end blind.

The third type is the case in which the lower end of the esophagus communicates with the trachea and the upper end is blind; that is the most common type.

The fourth type is one in which both the lower and upper ends enter the trachea.

Dr. Donovan has told you of taking x-rays without the use of contrast media. It is well to get your data without the use of contrast media, but in these cases it is *imperative* not to use contrast media. You can see what happens when you give barium to any one of these patients. If you give it to patients with the first or third type, the barium goes into the upper blind end and comes up immediately, spills over, and gets into the trachea. In the case of patients with the second and fourth types, you pour barium through the fistula directly into the trachea and lung.

In the first type, without the use of contrast media, you will find no gas whatever in the abdomen and you will find regurgitation immediately following the ingestion of foods. With that and the combination of no gas in the abdominal cavity, you can be fairly certain of what you are dealing with.

In the second type the same thing is true, except that when you give fluid you immediately get difficulty with respiration, cyanosis, and so forth.

In the third type, which is in great contrast to the first type, every breath the child takes forces air into the intestinal tract and you find the whole intestinal tract distended with gas. That type is easy to diagnose from the x-ray without the use of contrast media.

The first type offers the best chance of initial anastomosis. We approach it through the right side of the back by making an incision over the third or fourth rib, excising those ribs and cutting the rib above and the rib below and pushing the pleura forward so as to enter the posterior part of the mediastinum. The two ends of the esophagus may be anastomosed. The difficulty with these cases is that the ends are apt to be far apart and the ends of the esophagus are difficult to suture together. I have heard indirectly that Dr. Haight of Ann Arbor has one of these patients with an anastomosis who is alive. That is the only one I know of.

We had two patients whom Dr. Lanman has so treated by direct anastomosis, and they lived for several weeks. We thought they were going to get well but they died from a combination of pneumonia and mediastinitis.

Last year we had a very interesting case, our only patient who is living (third type). A gastrostomy had been done in another city. It was soon evident that whenever food was put in through the gastrostomy some of it went upward into the lung and the child got an aspiration pneumonia. This patient was one of those unusual children who really had a lot of resistance and who recovered from several bouts of pneumonia.

Our first step was to tie off the tracheo-esophageal fistula. The child was in precarious condition and we did not undertake to do anything more. This was done to prevent food from going up into the lungs. We then could feed the child through the gastrostomy tube without difficulty.

The next operation consisted of bringing out the upper blind end of the esophagus onto the left side of the neck, just above the clavicle. That is an important procedure to get done as early as possible, because these children swallow saliva even if they are given nothing by mouth. It fills up this esophageal pouch, and constantly spills over into the lungs. Even if you do not give them food by mouth, they get an aspiration pneumonia from this cause. After the upper esophageal pouch had been exteriorized and opened on the neck, we had a breathing spell in which we could let the child go along with feedings through the gastrostomy tube. The pneumonia eventually cleared up and the baby eventually attained a good physical condition.

Our final steps have been aimed at building an anterior thoracic esophagus. It is interesting to see this child now. He has an exterior, subcutaneous, skin-lined esophagus which comes within an inch or so of the gastrostomy, and it is fun to give this child orange juice, milk, soup, or anything else, and see it go through with the most surprising rapidity. In fact, saliva is going through all the time. I plan to join up this anterior thoracic esophagus with the gastrostomy, a process which might not be so simple, since it involves rather technical details which we need not enter into here for the moment.

In the future I think we will be able to take better care of these patients than we have in past years.

QUESTION.—How do you calculate the dosages of parenteral fluid, blood, and plasma which are to be administered to the patient with intestinal obstruction?

DR. GROSS.—The correction of fluid imbalances is just as important in the care of a patient as is his operative procedure. It is sometimes a long and tedious treatment which requires a great deal of attention, time, thought, and patience.

It is probably well to begin the use of parenteral fluid rather dogmatically. We base its administraiton on the body weight. Ten per cent glucose in water is injected intravenously (10 c.c. per pound of weight) and this is immediately followed by a hypodermoclysis of physiologic saline (15 c.c. to the pound). Generally, two such sets are given in each twenty-four hours for the first two or three days. Such dosages are usually sufficient to carry an average patient along.

There comes a time after forty-eight or seventy-two hours when one might find that the above regime gives too much fluid or salt, or not enough of these substances. It therefore becomes imperative to alter the regime as the requirements of the individual might demand. Several factors must be considered. First of all, the patient may have a fever and need more fluid because of loss through excessive perspiration. There may also be an enterostomy which discharges great quantities of electrolytes and fluids. Most of such patients have a gastric suction tube in place, so that the duodenal or gastric juice is being aspirated. All of these add up to a considerable loss of fluid and salt, materials which are quite necessary and which must be replaced. Hence it is important after twenty-four to forty-eight hours to re-evaluate the fluid balance situation critically. The best way to do this is by clinical examination of the patient. It is not essential to have a complicated laboratory study at this stage. In the usual examination we observe the dryness or moisture of the tongue and skin, determine how often the individual has urinated, and how much urine is being passed. By such means we can get a rough idea of the balance the individual might be in. It is desirable to keep some sort of a written sheet on which are tabulated the individual's intake and output. It enables the physician to find out quickly what the fluid balance is for any twenty-four-hour period.

There comes a time after three or four days when the above-mentioned simple observations do not give sufficient data to permit an accurate appraisal of the patient's condition. By this time it is important to determine two things: (1) the level of the serum chloride, and (2) the level of the plasma proteins. When one

is dealing with an individual with obstruction and a greatly disturbed fluid loss and intake, it is rather imperative after the first few days to employ these two laboratory determinations. There is just as much danger in giving too much chloride as there is in allowing the blood chlorides to get too low. If one gives too much chloride by parenteral routes, cardiac edema, cerebral edema, and peripheral edema may develop. Plasma protein must be kept at a reasonably high level to prevent edema and to promote wound healing.

When an individual has been starved before operation and is not able to take food by mouth for some time after operation, he is very apt to have his blood protein fall to a dangerously low level. Protein can be restored by the use of blood, which is given if the red count is low. If, however, the red count is sufficiently high, the protein can be restored by using plasma. Under urgent conditions plasma can be administered two or three times in each twenty-four-hour period.

Summing up this fluid situation, one can say that in the first twenty-four or forty-eight hours standard doses of fluid can be given empirically, but that after the two-day period one has to change and increase or decrease the fluids according to the requirements of the case. After three or four days, it is essential to determine the level of blood chlorides and protein to determine just how much chloride, plasma, and blood one should give.

CHAIRMAN LADD.—We have several questions turned in on malrotation of the intestines. The subject of malrotation has interested me very much, and I think the quickest and easiest way to attack the problem is to summarize rather quickly the reasons why malrotation causes obstruction and then show what can be done in the way of treating such obstructions.

The obstruction from malrotation or midgut volvulus always takes place at the duodenum first, and then as the volvulus comes through an arc of 180 degrees or 360 degrees another obstruction also takes place in the transverse colon. Hence, in the early stages of obstruction from malrotation you must not expect generalized abdominal distension because it is a duodenal blockage. The only distension present is in the proximal part of the duodenum, and as the child vomits, even this becomes deflated. I think that is an important factor to emphasize, as Dr. Donovan has mentioned before.

(Slides showing embryology of malrotation.)

The first slide illustrates the fact that during the first and second weeks of fetal life the intestine develops very much more rapidly than the abdominal cavity. The result is that there is not room enough in the abdominal cavity to accommodate all of the alimentary tract. Nature meets that situation by allowing the intestine to bulge out forward into the base of the umbilical cord and producing what one might term a temporary physiologic omphalocele. Practically all of the midgut goes out through the umbilical rim into the base of the umbilical cord. About the sixth or seventh week of fetal life the midgut starts to return, and it returns in a particular manner. The superior segment of the midgut, that is, all of the intestine which is above the vitelline duct, goes in first and it goes to the left. That is followed by the inferior segment, including all of the remaining midgut from the vitelline duct down to the middle of the transverse colon. Then the colon starts its rotation in a counterclockwise direction so that the cecum travels from the left upper quadrant across the duodenum and eventually descends into the right lower quadrant.

An arrest in movement may take place at any time during the above-described progression and repositioning of the intestines and colon. If the mass of intestines stays in the umbilical cord, one has an omphalocele which presents a difficult but a

surmountable surgical problem. If the intestines get back into the abdominal cavity and become arrested at any stage of rotation, obstruction of some type almost always results.

If the cecum becomes arrested as it crosses the duodenum, the latter is pressed upon and partially obstructed.

It is important to remember that these patients have only a rudimentary attachment of the mesentery to the posterior abdominal wall; hence the small gut is free to rotate in any direction. Thus, in about half of the patients a volvulus takes place. This is usually in a clockwise direction but on rare occasions it can be in a counterclockwise direction.

Here is the simplest form of obstruction due to malrotation. In this particular case the symptoms came on rather late in life. If I remember right, the girl was 9 or 10 years old before she had very many severe symptoms. She was always below par, always undernourished, always had a finicky appetite, and complained of mild pain with occasional little vomiting, but she did not get her acute obstruction until she was 9 or 10 years old. Then she got an obstruction at this point [indicating the duodenum]. The first part of the duodenum was greatly dilated. All one has to do in treating such a patient is to make an incision in the posterior parietal peritoneum and transfer the cecum toward the patient's left so that it is shifted off the duodenum.

(Lantern slide)

In this operation, we do not attempt to restore normal anatomical conditions. What we want to do is to restore the health of the child. If the cecum is transferred and the whole duodenum is exposed, the obstruction is relieved, and the physiologic function is restored, which is all we are interested in.

(Lantern slide)

Here is a form of midgut volvulus. I think this should be understood not only by pediatricians but also by surgeons, and I think there are few surgeons who really do understand it. It is a very confusing situation if one does not remember the embryology. When the abdomen is opened one cannot see anything where it ought to be—indeed, everything is where it ought not to be, and the surgeon is apt to be quite confused. I have seen several autopsy specimens of patients who have been operated upon, and the surgeon, not knowing what to do, sewed up the abdomen in despair, and the child died of intestinal obstruction.

(Lantern slide)

When one opens the abdomen one sees a picture like this drawing [indicating]. The intestine is a little dusky in color. One cannot see the colon and one does not see the cecum at all. They are covered by the loops of the twisted midgut. It is imperative to deliver the whole midgut outside the abdominal cavity, and then one sees what he is dealing with.

In the next drawing one sees the midgut delivered out of the abdomen, and the twist of the mesentery base is now obvious. The first procedure is to untwist the volvulus. One starts untwisting and almost immediately the colon and intestine assume a normal color. At this point the inexperienced operator is prone to think that he has done enough. But that is not true. It has been shown by us, and Dr. Donovan has had the same experience in New York, that if one merely unturns the volvulus the operation is not complete, and one finds bands across the duodenum which are still causing obstruction. This duodenal obstruction must be relieved if the child is to be cured. Hence, after reducing the volvulus, an incision is made in the posterior peritoneum and the cecum is allowed to slide off the duodenum until the duodenum is completely exposed.

(Lantern slide)

Just to prove that I am not fibbing to you, here are the results we have had from various types of surgical procedures in these cases.

Among our first cases were four patients who were treated *only* by reduction of the volvulus; there was 100 per cent mortality.

Some patients were treated by an anterior gastroenterostomy, since it was thought that the duodenal obstruction could be satisfactorily relieved by short circuiting it. This operation gave 100 per cent mortality also.

Then we adopted the type of operation which I described above, namely, undoing the volvulus first and then relieving any external pressure on the duodenum. With such a procedure we have had 35 cases with 27 recoveries.

News and Notes

At the Fifty-Fourth Annual Meeting of the American Pediatric Society at Skytop Lodge, Skytop, Pa., April 30 to May 2, 1942, the following members were elected officers for 1942-43:

Dr. James L. Gamble, Boston, Mass., President
Dr. S. Graham Ross, Montreal, Quebec, Vice-President
Dr. Hugh McCulloch, St. Louis, Mo., Secretary and Treasurer
Dr. Heyworth N. Sanford, Chicago, Ill., Recorder and Editor
Dr. James D. Trask, New Haven, Conn. (Deceased), Councilor

The following candidates were elected to membership in the Society:

Dr. Hattie E. Alexander, New York, N. Y.
Dr. Bert I. Beverly, Chicago, Ill.
Dr. William C. Deamer, San Francisco, Calif.
Dr. Parker Dooley, Chicago, Ill.
Dr. Sidney Farber, Boston, Mass.
Dr. Harold E. Harrison, New York, N. Y.
Dr. Lee F. Hill, Des Moines, Iowa

At the meeting of the Executive Board of the Academy, it was decided that unless circumstances developed which were adverse to holding the annual meeting of the Academy, the meeting would be held. It is decided, therefore, to go ahead with the plans for the meeting at the Palmer House, Chicago, Ill., Nov. 4-7, 1942.

It seems desirable that such a meeting should be held because of the many problems with respect to the children of this country and Canada which are sure to come up in the not distant future. The place where these can get the widest recognition and most helpful consideration is at the annual meeting of the American Academy of Pediatrics.

Dr. James D. Trask, of New Haven, Conn., died on May 24 in Chicago. He was on a task commission examining epidemiologic conditions in the army military camps in the Chicago area when stricken suddenly with an acute abdominal infection.

Dr. Trask was Associate Professor of Pediatrics at Yale University, having been Assistant Professor of Medicine previously. He had been continually interested in the field of infectious and communicable diseases. He had studied particularly the streptococcal infections and recently had made important contributions to the epidemiology of poliomyelitis. He served in the army during World War I. Because of his ability, he had been chosen as special consultant to the War Department and was working as a member of the Commission on Hemolytic Streptococcal Conditions. His sudden and unfortunate death interrupted a brilliant career and will be a loss to his country, the medical profession, and his fellow workers.

Dr. Trask was a member of many societies. He was a member of the American Pediatric Society, of which he had just been elected a member of the council, and the Society of Pediatric Research; also, the Association of American Physicians, the American Society for Clinical Investigation, the American Clinical and Climatological Association, and the Society of American Bacteriologists.

The following internships and residencies are offered on the Children's Medical Service of the Massachusetts General Hospital:

The one-year internships include: (1) three months on the children's service at the Massachusetts Eye and Ear Infirmary and the children's medical outpatient and the emergency ward of the Massachusetts General Hospital (total, 50 beds); (2) three months at the Haynes Memorial Hospital for Communicable Disease (150 beds); (3) three months on the children's ward (17 beds); and (4) three months on the infants' ward (20 beds) of the children's service of the Massachusetts General Hospital. Additional experience in the care of the newborn infant is provided each intern through the supervision of the newborn nursery of the Florence Crittenton Home (30 beds).

The one-year residencies include supervision of the medical care of the pediatric patients on the following services: (1) the infants' and children's wards of the Massachusetts General Hospital; (2) the emergency ward of the Massachusetts General Hospital; (3) the infants' and children's wards of the Massachusetts Eye and Ear Infirmary; (4) the newborn nursery and pediatric division of the Baker Memorial, which is a private hospital for patients of medium income (averaging 30 pediatric patients). For residents living in the hospital, the remuneration is $500 a year. Special arrangements are made for residents living outside the hospital.

The Commonwealth Fund of New York, a philanthropic foundation established in 1918 by the late Mrs. Stephen V. Harkness, announces that it is offering through the Pan-American Sanitary Bureau fifteen fellowships for one year's study of public health subjects or postgraduate medical courses to properly qualified persons who are citizens of the other American republics. Fellowships in public health will be open to physicians, sanitary officers, technicians, public health nurses etc. These fellows will be selected through a system of cooperation with medical and health authorities of the different countries concerned, and whenever deemed advisable they will be interviewed by traveling representatives of the Pan-American Sanitary Bureau. Each fellowship will provide living allowances while the holder is in the United States, travel costs, and tuition. Knowledge of the English language will be among the requirements, and also the possession of certain specific qualifications.

The Pan-American Sanitary Bureau, the international health agency of the American republics, has been for some time the recognized clearing house for medical and public health fellowships in the United States, nearly one hundred Latin Americans now being in the United States under its auspices.

Application blanks giving complete information will be available through the Commonwealth Fund, 41 East 57th Street, New York; the Pan-American Sanitary Bureau, Washington, D. C.; or chiefs of American Missions in Latin America.

Book Reviews

Management of the Sick Infant and Child. Langley Porter M.D., and William E. Carter, M.D., ed. 6, St. Louis, 1942, The C. V. Mosby Co., pp. 977. Price $11.50.

Porter and Carter's "Management" is so well known that an extensive review is unnecessary. The sixth edition is a thorough revision, and the volume is over one hundred pages larger than the fifth edition, which was published in 1938. Nearly every chapter has been revised to include the many advances made in medical science in recent years. The book remains fundamentally practical, and the continued demand for new editions reflects its established position with the medical practitioner.

From Infancy Through Childhood. Louis W. Sauer, M.D., New York City, 1942, Harper & Brothers, pp. 200. Price $2.00.

A new addition to the many books on the Care of the Baby. If any criticism in particular is to be made of Dr. Sauer's book, it is that it seems a trifle too technical for the average mother. In general, it is no better and no worse than the usual run of this type of book. We have still to find one better than the ten-cent pamphlet published by the Government.

Nursing of Children. Gladys Sellew, Ph.D., R.N., ed. 5, Philadelphia, 1942, W. B. Saunders Co., pp. 579. Price $2.75.

The fifth edition since first published in 1926. Perhaps the most striking parts of this well-known text are the "Second Unit," which covers the growth and development of children and its related nursing implications, and the "Third Unit" on the general nursing of children. The balance follows the usual more or less stereotyped discussion of diseases, milk preparation, feeding, etc. A thorough revision and a condensation of this material would have improved the book as a whole. For example, such important items as the discussion of diphtheria immunization could have been made more complete, and a discussion of immunization in tetanus and pertussis, which are omitted, could have well been introduced in place of a discussion of "percentage feeding" which is only a matter of historical interest. The family nursing technique discussion is admirable.

The Prevention of Deformity in Childhood. R. B. Raney, M.D., and A. R. Shands, M.D., Elyria, Ohio, 1941, National Society for Crippled Children, pp. 188. Price $1.00.

A primer on the prevention of deformity in children designed for those who first see the child with a condition which may result in deformity. This stressing of the preventive angle of orthopedic surgery is most important. The information is given simply and clearly. First the affections in childhood which may cause deformity are discussed, and this is followed by a discussion of deformities by regions, as upper extremity, lower extremity, etc. The text is fully and excellently illustrated with some 808 drawings.

Cabot and Adams. Physical Diagnosis, ed. 14, Baltimore, 1942, Williams & Wilkins Co., pp. 888. Price $5.00.

Any text which has gone through thirteen editions since it was first published in 1900 well deserves the reputation of a standard authoritative text. The reviewer

well remembers the second edition as his introduction to clinical medicine many years ago, and it is interesting to muse over the number of American physicians today who have been influenced by this text. The book has been reviewed so many times that a detailed description is unnecessary. Sufficient to say that Dr. Adams has in his changes kept abreast of new methods and of new interpretations of physical findings. The most important revisions are in the field of the cardiovascular system.

Pediatric Gynecology. Goodrich C. Schauffler, M.D., Chicago, 1941, The Year Book Publishers, Inc., pp. 384. Price $5.00.

This book is the "first and only" of its kind. It is a sure-fire "must" for every pediatrician's library. It is fortunate that the inspiration to produce such "first and only" fell on such fertile soil, for the author has achieved a more than usual result in filling the need for a book in this field of pediatrics. On every page one can feel the personal qualities of the author, his judgment in selecting only the most reliable information, in expressing his thoughts and feelings clearly, and in evaluating the general knowledge in the field of normal anatomy, physiology, and developmental processes as well as the pathologic conditions relating to the female child's genitourinary and reproductive system. He has been very successful in uniting the subject matter closely to the pediatric field of gynecology.

Before preparing this review, the book has been discussed with an eminent gynecologist, who is himself well informed in this field, for his opinion as to its value and correctness from the gynecologic viewpoint. He has given assurance that the book is reliable and entirely correct in all the principles and ideas set forth. The material represents more gynecologic pediatrics than pediatric gynecology, and it was agreed that the book might be more useful to pediatricians than to gynecologists, but that both groups should find ample satisfaction from reading it.

This reviewer finds the contents most satisfactory from two standpoints: first, the discussion of the psychologic factor in the management of children and in special methods and technique necessary in an investigation of this type of examination; second, the great emphasis that is placed on the phase of growth and development of the reproductive system of the child and the relation of this phase to the child as a whole. The most advanced and profound thinking pediatrician will find himself in full harmony with the ideas expressed by the author and the manner in which he deals with the subject. Considerable emphasis is given naturally to the child during the adolescent period, a period which is still somewhat vague and poorly dealt with by a large group of pediatricians. A short chapter of only six pages deals with surgical considerations, principally preoperative and postoperative. There is no presentation of operative technique other than those concerned with the physical examination. Besides a chapter on urologic conditions, there is also one on proctologic conditions, a field that certainly is not often described in a pediatric text. One will find also a most thorough and thoughtful presentation of the management of a girl during the onset of menstruation with treatment of special difficulties.

The book is unusually well illustrated. The author's style is a pleasure to follow, and the pages are full of striking and interesting statements.

McCULLOCH.

Medical Genetics. Laurence H. Snyder, Sc.D., Durham, N. C., 1941, Duke University Press, pp. 130. Price $1.50.

This book is based on a course of lectures which was given to the sophomore class at the College of Medicine of Ohio State University, and which was expanded, somewhat rearranged, and presented in 1941 to the entire student body of the medical schools of Duke University, Wake Forest College, and the University of North

Carolina under the auspices of the Carnegie Corporation. In such short series of lectures on medical genetics it was not possible to give an adequate account of the basic principle of genetics. The material in this book, therefore, deals strictly with medical conditions and their practical application.

The author outlines the more important kinds of hereditary behavior in such a way as to make them understandable. This has been done in connection with specific trends the first time that each major kind of hereditary behavior is encountered. Chapter IV, in which the various genetic mechanisms are first met in connection with eye abnormalities, provides a working acquaintance to the main kinds of genic action. Following some general principles in Chapter I, and the medicolegal application of hereditary traits in Chapter II, the various medical conditions are discussed system by system. The book is very brief, clear, and useful to anyone not familiar with the field of genetics. Its elementary form is the necessary result of preparing a book on the subject for the audience to which it is addressed. For this very reason it should be of interest to pediatricians and practitioners. It should serve a still more useful purpose in arousing a greater interest in this important field of medicine. The book can be read in three hours, but one finds a lingering satisfaction in thoughtful consideration of its contents and wishing for further knowledge.

McCULLOCH.

Directory of Medical Specialists. Ed. 2, New York, 1942, Columbia University Press, pp. XVI + 2495. Price $7.00.

Since the first edition appeared, more than four thousand doctors have taken their Board examinations. This second edition, therefore, contains complete information about more than eighteen thousand diplomates. Not only is the book larger by that many diplomates, but also information about each doctor is more complete than it was before. An idea of the increase in size of the second edition may be indicated by the increase from 1,573 pages in the first edition to the present 2,495 pages. The pediatric section shows an increase from 110 pages to 181 pages.

This book is not only a directory to medical specialists, but also an index to a trend in medical development. The value of the book to a nation at war is tremendous. To Washington officials, to army and navy administrators, as well as to local and regional selective service executives, it will become increasingly useful.

A separate section is devoted to each American Board, with both a geographic and a biographic listing of its diplomates. In addition, there is a complete alphabetic list of all diplomates. In this list there are addresses and indications of specialty certification, while in the geographic section complete biographic information is given. The organization and examination requirements of each of the American Boards are explained in full. All these features make the directory unique and invaluable to doctors (specialists or general practitioners), hospitals, social agencies, libraries, medical societies, business organizations, etc. It will help hospital officials pass on the ability of candidates for staff positions; it will provide medical society officers with authoritative lists; and the family physician can form accurate judgment of the qualification and ability of specialists in any branch of medicine for the benefit of his patients.

The book in general has the same arrangement and form as the first edition. It is now four years since the first edition appeared. During this time the various Boards have probably "cleaned up" the last available but delinquent specialists who had not been included in the first edition. Since these names have been added to ed. 2, further increase in size of future editions should not be so great. Accessions will outnumber deletions probably only slightly. The book is an indispensable directory.

McCULLOCH.

The Modern Attack on Tuberculosis. Henry D. Chadwick, M.D., and Alton S. Pope, M.D., New York, 1942, The Commonwealth Fund, pp. 95. Price $1.00.

The chief purpose of this concise handbook is to promote the effective use of known methods for detecting and controlling tuberculosis, which, without future additions, are adequate for the eventual eradication of the disease. In outlining the various phases of the problem of tuberculosis control and the operation of effective regional programs, the authors stress basic principles rather than the exact methods that have proved productive.

Six concise chapters present sound appraisals of (1) the measures that have contributed to the control of tuberculosis; (2) the epidemiology of the disease; (3) the essential diagnostic procedures and their use; (4) the function of the sanatorium in the control program; (5) case finding in the community; and (6) a communnity program for the eradication of tuberculosis.

The authors are eminently qualified to analyze the modern attack on tuberculosis and have produced a conservative, practical, concise, and sound discussion of the subject. They make no pretense, however, of adding to the sum of our knowledge of tuberculosis.

Public officials, physicians, nurses, and others interested in the control and eradication of tuberculosis will find this inexpensive booklet useful as well as brief.

STEWART.